Surgical Pathology

By

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"As is our pathology so is our practice," OSLER

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FOREWORD

Each generation builds from the shoulders of the generation before. The pioneer pathologists of the past generation laid a foundation for the science of pathology which was very important, but their knowledge of pathologic conditions was acquired largely from the postmortem room. Even specimens removed at biopsy were cadaverized before they were submitted to microscopic examination. Today pathology is a science dealing with living things and conditions. It furnishes a groundwork of knowledge which facilitates early diagnosis of disease in the living, and its cure by scientific methods.

What is needed today in the literature of surgical pathology is a work that will serve as a handbook to the surgeon, and the internist, and a guide to the beginner in the field of medicine. Dr. Boyd has made an earnest effort to fill this need. His book is didactic in tone, as is necessary in a volume of this scope, not judicial, fortunately, because to be judicial one must deal only with proved facts and give no play to scientific imagination. It is a sincere attempt to place pathology before the student and the practitioner from the practical standpoint.

WILLIAM J. MAYO

PREFACE TO THE SIXTH EDITION

The years which have elapsed since the last edition of this book appeared have for the most part been war years. During this period many technical advances have been made in surgery, particularly in relation to the treatment of wounds. It is curious, however, that the most dramatic addition to knowledge has been in a field which has hitherto been considered entirely outside of the realm of the surgeon, namely the treatment of congenital heart disease. For that reason an entirely new section has been added dealing with the pathology and pathological physiology of that condition.

Other new material includes tumors of the larynx, pinealoma, Bittner's milk factor in relation to breast carcinoma, avitaminosis in cancer of the mouth, the Papanicolaou vaginal smear method in diagnosing carcinoma of the cervix, fibrous dysplasia of bone, inflammatory nodules of muscle in chronic arthritis, and fibrositis of the back. In the last-named condition, so common and so disabling, some of the new work holds out relief to the great army of sufferers.

I am greatly indebted to Miss H. J. Williamson and Miss N. W. Simpson for assistance in seeing the work through the press.

WILLIAM BOYD

PREFACE

The object of this book is to present those aspects of pathology which will prove useful to the surgeon. Modern surgery is based on pathology as much as on anatomy, but the ordinary text-book of pathology contains a large amount of material of little interest to the surgeon, and it often lacks a detailed discussion of the very subjects regarding which he is seeking information. In the present volume an attempt is made to meet this want.

The treatment of the various subjects may appear uneven, but this is because we have tried to maintain a reasonable balance between the common and important conditions and those which are rare and of less importance. To treat every condition at equal length conveys an entirely wrong sense of proportion to the reader. Further information on the more recondite subjects can be found in the references at the end of each chapter.

A list of references may be so long as to defeat its own object, which is not to display the erudition of the writer, but rather to induce the reader to go further afield in his search for knowledge. In preparing the present work the writer has considered that his object would be best served by giving only the most important references, and those mostly in English, except where the information cannot be obtained in that language.

Although not strictly in place in a work on pathology, the clinical features of most of the conditions have been summarized, so that the relation of the pathology to the symptomatology could be demonstrated. The chapter on Surgical Bacteriology is intended to be of use to the surgeon, not to the bacteriologist. It is hoped that the directions for the collection of pathological material, so generally neglected, will prove of value.

The pathological and surgical treatises to which the author is indebted are too numerous for acknowledgment, but he would in particular mention the pathological sections in Keen's Surgery and Ewing's monumental work on Neoplastic Diseases. The basis of the work has been the surgical material examined in the Pathological Department of the Winnipeg General Hospital, the living pathology observed in the operating rooms, and the specimens contained in the Pathological Museum of the University of Manitoba. As far as possible the pathological descriptions have been based upon a study of this material rather than upon the observations of others.

WILLIAM BOYD

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CHAPTER I

SURGERY AND PATHOLOGY

"As is our pathology so is our practice."—Osler

The surgery of to-day is based on pathology. Unless he builds on that solid foundation the surgeon is no better than a hewer of flesh and a drawer of blood.

It has not always been so. We do not need to look far into the dark backward and abysm of time to realize that the foundation of surgery was the sand of empiricism rather than the bed-rock of pathology. A brief survey of the surgical achievements of the great ones in the history of medicine will show that these, often wonderfully brilliant, lacked the sure basis which could make possible further progress to fresh triumphs, although here and there struggles towards the light can be detected.

Long before the Christian era the Egyptians and many others used to trephine the skull for migraine and epilepsy: a remarkable tour de force, but one which could not be followed up. Hippocrates himself, with all his marvellous powers of observation, with all his clinical acumen and daring as a surgeon—was he not the first to tap the hydrocephalic ventricle?—was grievously handicapped by his ignorance of morbid anatomy.

The great Galen caught a glimpse of the true road to progress and set his foot upon it, for he it was who first introduced experimental methods into medicine, and advocated a consideration of the pathological basis of the disease in determining the appropriate surgical treatment. The man who could observe the effect on the larynx of experimental division of the recurrent laryngeal nerve, who could demonstrate the relation between hemiplegia and hemisection of the spinal cord in a dog, was no mere empiricist. But for more than a thousand years the good seed lay on barren ground, or was choked with weeds.

Even Ambroise Paré, that great clinical surgeon of the 16th century, stumbled upon his method of treating wounds in a purely empirical way. He used to treat gunshot wounds after the manner of his day by plunging the limb into boiling oil, but on one occasion his supply of oil ran out, and he found to his surprise that the wounds treated with a simple ointment did much better than those to which the orthodox heroic measures had been applied. A great step forward, but certain progress was not possible as long as it was dependent upon such happy chances.

In the history of human progress there appears now and then a thunderbolt, and the thunderbolt of surgery is John Hunter. The history of surgery may without exaggeration be divided into two periods—before Hunter and after. Before him it was content to be an art founded on empiricism; after him it aspired to be a science founded on pathology. He was the first and greatest surgical pathologist. Surgeon, anatomist,

physiologist, pathologist, all in one, he towered above his contemporaries like a colossus. From that day the term surgical pathology came to have a real meaning.

It is true that the embryo surgeon of to-day does not always admit that the road to success must lead through the study of pathology. He may be tempted to turn away with a gesture of intellectual fatigue from the tiresome details of morbid anatomy and histology which can only be mastered by years of labor. To learn technic is easy, but to acquire judgment, based so largely as it must be on pathological knowledge, is a very different matter. He who prides himself on being a practical surgeon may be "ever learning, and never able to come to a knowledge of the truth." Such a one is given to peruse the statistics of end results, bristling with sources of fallacy, instead of looking into pathology for guidance in the difficult art of practice. A first-hand knowledge of pathology is the only safe guide for the hands of the surgeon, however skilled those hands may be.

The surgeon himself must be something of a morbid anatomist. He should be absolutely familiar with the gross appearance of diseased tissues. When he operates on a lump in the breast he must be able to say whether the cut surface indicates carcinoma, fibroadenoma, or chronic mastitis. It is an unfortunate tendency of modern medicine to depend too much upon the laboratory, to send the tissue there and await a diagnosis. If a pathologist be available a rapid tissue diagnosis may be made in the course of the operation, a procedure of inestimable value, but if such help is not available the surgeon must be his own pathologist and decide on the proper course to follow from the gross appearance of the tissue.

The microscopic side of pathology also demands attention, and the surgeon can develop a radiographic vision which will pierce through the skin, the deep fascia, the muscles, down to his bones themselves, nay, to the very bone cells which he can watch in his imagination as they marshal their forces, and commence to lay down new bone. Such a one can direct his treatment along rational scientific lines, and need no longer be bound by the shackles of empiricism. That a sound surgical judgment is based on a comprehension of pathological conditions is the first and greatest argument in favor of a study of pathology by the surgeon.

The fundamentals of pathology must be learned in the post-mortem room. There it is that the effects of disease are seen in their nakedness, and mistakes in diagnosis and surgical treatment are laid bare. The disease process can be seen as a whole, and the clinical picture viewed in a way that will often make light the dark places of the case. A tumor of the liver is found to be secondary to cancer in the rectum, the spread of a carcinoma can be traced from the stomach down over the peritoneum to the ovary, an infarct of the lung is seen to be due to thrombosis of the pelvic veins, a cerebral abscess is found to be secondary to an unsuspected bronchiectasis.

The pathology of the past has been built almost entirely on the findings of the post-mortem room, and the medicine and surgery of to-day bear the indelible imprint of that origin. And yet such a method has its shortcomings. The dead-house reveals only the end of the disease

process, often only the burnt-out volcano. But surgery is concerned more and more with the beginning rather than the end, for in the beginning here is hope, but in the end too often nothing but despair. To pluck out the weeds of disease they must be recognized in the early stages, else they may so overrun the garden, so deep and branching may become their roots, that eradication is impossible. A breast or a uterus infiltrated with carcinoma, a kidney or a knee joint disintegrated by tuberculosis, are interesting and important objects with whose appearance the student must become familiar. But they convey small hint of the beginning of the process; from them it is difficult or impossible to picture the initial lesion; they are conditions which all can diagnose but for which little can be done.

To the surgeon, then, rather than to the pathologist we are indebted for the conception termed by Moynihan "the pathology of the living," a phrase connoting the study of disease processes as seen in the living body in the operating room. There is, of course, but one pathology, and the expression will not bear too close a scrutiny, but it cannot be denied that a somewhat one-sided view may be acquired from an exclusive study of post-mortem material. A beginning only has been made, but who can doubt that great additions to pathological knowledge will come from the surgeon able to detect the early lesions of tuberculosis of the kidney, sclerosis of the pancreas, and malignant disease of the stomach?

No such contributions, however, are possible without a sound understanding on the part of the surgeon of things pathological. Without that, as Osler says, he will flounder along in an aimless fashion, hitting now the malady and again the patient, he himself not knowing which.

CHAPTER II

INFLAMMATION AND REPAIR

Inflammation is the most important as it is the most universal of all pathological processes. Being the *local reaction of the living tissues to an irritant*, it follows that some degree of inflammatory change is present wherever the tissues are subjected to the action of an irritant. No matter, therefore, how aseptic an operation may be, it must inevitably be accompanied by some degree of inflammation.

Irritants may be physical, chemical and bacterial. The commonest *physical* irritant is trauma, which includes the knife of the surgeon. Other examples are burns, frost bite, irradiation (X-rays and radium), a foreign body, etc. *Chemical* irritants such as poisons, strong acids and alkalis most often act on mucous membranes and skin. *Bacteria* are the chief cause of inflammation in surgery. They may be pyogenic, *i.e.*, pus-producers, or cause a low-grade chronic inflammation, as is seen in the infective granulomas.

As the result of the inflammatory process is to neutralize the irritant, and as far as possible remove it from the body, the process itself is often described as a purposive one. We must not, however, allow teleological ideas to dominate our conception of what is a purely physico-chemical process. Certain changes are to be observed in the vessels, partly or wholly as the result of which certain of the constituents of the blood pass from the inside to the outside of the vessels. Both of these phenomena are due to purely physico-chemical causes, so that a mechanistic explanation will meet all the facts of the case, and there is no justification for introducing a purposive or transcendental conception.

Our comprehension of the inflammatory process is based upon the researches on phagocytosis with which the name of Metchnikoff will always be associated. It was Metchnikoff who showed that the introduction of an irritant into the body was the signal for certain of the wandering mesoblastic cells of the body to exert themselves to encompass its destruction and removal. At the time of his great discovery he was in no way interested in problems of immunity, being engaged on a zoological research into the intracellular digestion manifested by the mesodermal cells of the more lowly organized animals. It was not on the human body that these observations were made, but upon the transparent body of the star-fish larva. Metchnikoff introduced some rose thorns into this lowly organism, and next morning he had the delight of observing that they were quickly clustered about by the wandering cells whose function he had been trying to determine. In that hour Metchnikoff was transformed from a zoologist into a pathologist. The fundamental discovery had been made, and the passing years merely showed how fully this principle could be applied to the higher animals and to man. In the star-fish larva there is no vascular nor nervous system, so

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that we may say that the essence of inflammation is *the reaction of the mesodermal cells against an external agent*. The vascular and nervous changes are of secondary significance. As we ascend the animal scale the process becomes more complex, the development of a vascular system renders it more complicated, but even in man the object of all the intricate mechanism is the removal of the irritant by means of phagocytosis, although other humoral factors are introduced which will require to be duly considered.

The inflammatory process may be described as the formation of an inflammatory exudate, the function of whose cells is to destroy and remove the irritant. In the higher animals certain striking vascular phenomena are also present, but the object of these changes is merely to allow the wandering cells, which in these animals are for the most part contained within the vessels, to escape to the site of the irritant, which is nearly always extravascular.

There are three main phases of the inflammatory process, each with its specific duty. These are the vascular changes, the formation of the inflammatory exudate, and the process of repair.

I. THE VASCULAR CHANGES

The feature of inflammation which attracts the attention of the clinician and the patient is the change which occurs in the blood vessels. It is not the essential feature, for the process of inflammation may occur in a non-vascular tissue such as the cornea, but it is the outward and visible sign of the inward change which is taking place, and it is largely responsible for the clinical signs characteristic of the condition.

The vascular changes are best studied in some transparent tissue such as the web of the foot, the mesentery, or even better, the tongue of the living frog. The mesentery of the rabbit or guinea pig may also be used, but the technical difficulties are greater in the case of a warm-blooded animal. These changes were described by Cohnheim in 1877 with such vividness and force that I cannot do better than quote some of the passages from the original description in his Lectures on General Pathology.

"The first thing you notice in the exposed vessels is a dilatation, which occurs chiefly in the arteries, then in the veins, and least of all in the capillaries. With the dilatation, which is gradually developed, but which during the space of fifteen to twenty minutes has usually attained considerable proportions, there immediately sets in in the mesentery an acceleration of the blood-stream, most striking again in the arteries, but very apparent in the veins and capillaries also. Yet this acceleration never lasts long; after half an hour or an hour it invariably gives place to a decided retardation, the velocity of the stream falling more or less below the normal standard, and so continuing as long as the vessels occupy their exposed situation.

"This stage having been reached, the vessels are seen to be all of them very wide; a multitude of capillaries which were formerly hardly perceptible can now be clearly distinguished; pulsation is unusually conspicuous on into the finest ramifications of the arteries, while the flow is everywhere slower than normal, so that the individual corpuscles may easily be recognized. It is the veins rather than the capillaries that attract the

notice of the observer, for slowly and gradually there is developed in them an extremely characteristic condition; the originally plasmatic zone becomes filled with innumerable colorless blood corpuscles. The plasmatic zone of the veins is always occupied by scattered colorless blood corpuscles, which, owing to their globular form and low specific gravity, are driven into the periphery of the stream, and whose adhesiveness makes it difficult for them to escape from the wall once they have come into contact with it. It is obvious that this difficulty will be enhanced in proportion to the slowness of the blood-stream, and thus it is not surprising that a gradual accumulation of large numbers of colorless corpuscles should take place in the peripheral zone and here come to be comparatively motionless.
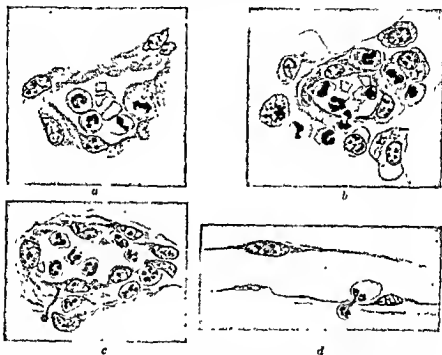

Fig 1.—Acute inflammation. *a*, Mitosis of endothelial cell in wall of small vein; *b*, *c*, and *d*, emigration of polymorphonuclear leucocytes through the walls of small blood vessels. (Mallory.)

The internal surface of the vein appears paved with a single, but unbroken, layer of colorless corpuscles, without the interposition at any time of a single red one.

"But the eye of the observer hardly has time to catch all the details of the picture before it is arrested by a very unexpected occurrence (Fig. 1). Usually it is a vein with the typical peripheral arrangement of the white corpuscles, but sometimes a capillary, that first displays the phenomenon. A pointed projection is seen on the external contour of the vessel wall; it pushes itself further outwards, increases in thickness, and the pointed projection is transformed into a colorless, rounded hump; this grows longer and thicker, throws out fresh points, and gradually withdraws itself from the vessel wall, with which at last it is con-

nected only by a long, thin pedicle. Finally, this also detaches itself, and now there lies outside the vessel a colorless, faintly glittering, contractile corpuscle, with a few short processes and one long one—in a word, a colorless blood corpuscle. Like every other stage of the entire process from the moment of exposure, these phenomena may develop either rapidly or slowly. At one time the earliest emigration very quickly succeeds the pavementing; at another an hour or more may pass without anything happening to draw attention to the contour of a single vein or capillary.

"Keeping pace with this exodus, emigration, or as it is also called, extravasation of corpuscular elements, there occurs an increased transudation of fluid, in consequence of which the meshes of the mesentery, or the tissues of the tongue, are infiltrated and swell. But this is not all. The extravasated leucocytes distribute themselves, in proportion as their numbers increase, over a large area, forsaking the neighborhood of the vessels from which they were derived. The tissues become more and more densely packed with them, while the red cells, which have not the power of independent locomotion, remain located in the vicinity of their capillaries. Soon a moment must arrive when the products of exudation and transudation can no longer be accommodated in the tissues. They now gain the free surface of the mesentery, and should the transuded fluid coagulate, as is the rule here, the final result of the processes just described will be the deposition on the mesentery as well as on the intestine, of a fibrinous pseudo-membrane, densely packed with colorless corpuscles, and interspersed with isolated red cells."

Such are the vascular phenomena of inflammation described by Cohnheim more than 70 years ago. A microscopic section of fixed tissue shows changes in the walls of the small vessels (venules and capillaries). The lining endothelium becomes markedly swollen so that the cells project into the lumen, and there is a loosening and separation of the elements composing the wall which renders more understandable the emigration of the leucocytes (Fig. 2).

The vascular changes are not intelligent responses, nervous in origin, but are due to the action of the irritant on the walls of the vessels. The walls of the small arteries and veins are of course largely composed of muscle, but the investigations of Krogh have shown that the capillaries are also actively contractile tubes. The dilatation of the vessels, with the accompanying engorgement and transudation, are due to the irritant paralyzing the contractile elements in the vessel walls.

Within recent years Menkin has published a series of experimental studies on the mechanism of inflammation, now collected into a monograph entitled "The Dynamics of Inflammation." He has succeeded in isolating chemical factors from experimentally produced inflammatory exudates, factors which appear to play an important part in the mechanism of the process. One of these factors, which he calls *leucotaxine*, induces a prompt increase in the permeability of normal capillaries. It seems to be an intermediary breakdown product of protein metabolism. When this substance is injected locally the increased capillary permeability is followed by the rapid migration of polymorphonuclear leucocytes. It is definitely chemotactic. Another factor in the exudate is

capable of causing marked leucocytosis in the normal animal. This factor does not appear to be related to leucotaxine.

Sir Thomas Lewis has suggested that a histamine-like substance, which he calls the *H substance*, is liberated at the site of inflammation, and that this is responsible for the increased vascular permeability. The evidence in support of this appears to be less conclusive than in the case of Menkin's leucotaxic factor.

Such in brief are the vascular phenomena of inflammation. What is their purpose? They provide the mechanism by means of which the in-
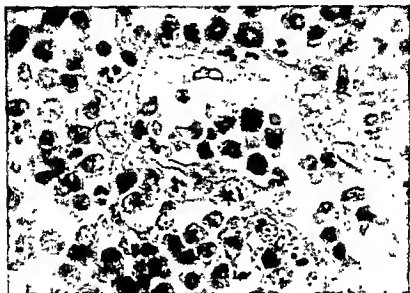

Fig. 2.—Leucocytes emigrating through vessel wall and accumulating in the tissues. × 700.

flammatory exudate is produced. The formation of that exudate is the sole object of the inflammatory process, so that the vascular changes in themselves are meaningless.

II. THE INFLAMMATORY EXUDATE

The inflammatory exudate is formed (1) by the migrating cells from the blood, (2) by the blood plasma, (3) by certain cells of the tissues. The purpose of the exudate is to neutralize and overcome the irritant, to remove it, and to repair the damage done. Attempts at repair, indeed, may begin early in the process, and the various stages may all be seen in the same tissue.

1. **The Blood Cells.**—The *polymorphonuclear leucocyte* is the cell of acute inflammation. In acute pyogenic infections it may appear to be the only cell present. The number in the circulating blood is greatly increased, a condition of leucocytosis, owing to hyperactivity of the leucoblastic tissue in the bone marrow. The characteristic appearance of its lobed or multipartite nucleus and the fine neutrophil granules of its cytoplasm are too well known to demand description. In the early stages the outline is well preserved and the nucleus sharp and distinct.

Later the cells become degenerated, indistinct, and stain diffusely. They constitute the chief element of pus, but as pus cells they usually show marked granular degeneration. On disintegrating they liberate proteolytic ferments. They are actively ameboid and phagocytic, and their chief function is the destruction of living bacteria by phagocytosis.

The *lymphocyte* plays but a minor part in acute pyogenic inflammation, although it may be present in some numbers in the later stages. In chronic inflammation, and especially in the infectious granulomata such as tuberculosis and syphilis, it assumes a position of commanding importance, and the tissue which is the site of the lesion may be packed with these cells. It must be admitted, however, that many, if not most, of the "small round cells" seen in chronic inflammation may be derived from the tissues rather than from the blood. The lymphocyte plays no part in the phagocytosis of bacteria or the removal of necrotic tissue, but it appears highly probable from the earlier work of Maximow and the later work of Kolouch that in acute inflammation the hematogenous lymphocytes become transformed into phagocytic macrophages. Kolouch observed this development hour by hour in imprints of the exudate resulting from the injection of egg albumin into the subcutaneous tissue of rabbits. In a little over twelve hours nearly all the lymphocytes had become large macrophages showing active phagocytosis. The change is so rapid that it is easily overlooked in tissue sections.

The *large mononuclear*, a cell larger than the lymphocyte, with indented or kidney-shaped nucleus and more abundant cytoplasm, cannot be distinguished in the inflammatory exudate from the vascular and other endothelial cells presently to be discussed. Indeed it is not improbable that the large mononuclears are derived from these cells. Their function is to act as scavengers in the later stages of inflammation, removing by virtue of their great phagocytic power the dead bodies of leucocytes, bacteria, and tissue cells, and carrying them away in the lymph stream. They are therefore present in small numbers in the early, but become much more numerous in the later stages of inflammation. In typhoid fever they, together with the endothelial cells, form the prominent feature, crowding the intestinal, glandular, and other lesions.

The *eosinophil* is a mysterious cell which appears in considerable numbers, but for no apparent object, in certain very diverse conditions. An eosinophilia in the blood is found in infection by animal parasites, in asthma, and in urticaria and other similar skin affections, all conditions in which an element of anaphylaxis plays some part. In asthma the bronchial mucous membrane may be crowded with eosinophils, and in many appendices the seat of chronic inflammation I have been struck with the extraordinary numbers of eosinophils particularly in the mucous and sub-mucous coats. As in the case of the lymphocyte, it is possible that many of these cells are derived from the tissues rather than from the blood.

Red blood corpuscles when present must be regarded as accidental. They have no function to perform, and have either passed through the openings made by the migrating leucocytes, or are due to rupture of the vessel caused by undue distension or by the toxic action of circulating poisons upon the vessel wall.

Phagocytosis.—The cells of the inflammatory exudate are collected about the irritant in order that they may have the opportunity of exercising their power of phagocytosis. The work of Metchnikoff has shown that phagocytosis is an almost universal endowment of cell life It is by this power that the cells of the lower organisms absorb their nourishment; by means of it even the most resistant tissue, such as bone, is moulded into shape; it is the mechanism by which dead tissues are removed from the body; and finally it is the most efficient defense of the body against disease.

In the acute stage of inflammation the polymorphonuclear leucocyte is the most active phagocyte (Fig. 3). It approaches the bacterium, pushes forth processes of protoplasm called pseudopodia or false feet, engulfs its prey, and digests it by means of the digestive ferment which it secretes. The absorbed body gradually disappears, and its former site is indicated by a digestive vacuole.

Other phagocytic cells playing an important part in inflammation are the large mononuclear leucocytes of the blood; the endothelial cells

lining the blood vessels, the lymphatics, and the serous membranes; and the wandering connective tissue cells. These cells, which may be grouped collectively as the mononuclear cells of the inflammatory exudate, usually direct their attention to the absorption of dead cells and tissues, such as defunct leucocytes and red blood cells, blood pigment, particles of bone, etc., but they may also contain bacteria, especially those responsible for the more chronic types of inflammation, such as tuberculosis.

Fig. 3.—Cocci within polymorphonuclear leucocyte. × 1500.

The task of removing these more chronic irritants sometimes leads to the formation of giant cells, which result from the fusion of a number of phagocytes to form one large cell containing numerous nuclei usually arranged around the periphery of the cell. These foreign body giant cells may be seen to great advantage when a foreign body such as a lycopodium spore is introduced into the tissues. They are present in tuberculosis, syphilis, actinomycosis, any form of bone destruction—in short in any condition where a somewhat refractory irritant has to be removed

The phagocytes which are unable to digest all that they have absorbed dispose of this material in several ways. Many carry it to the surface and discharge it on to an ulcer; many pass into the lymphatics and deposit it in the lymph glands; some retire into the blood stream and find a grave in the spleen, the liver, and other cemeteries of the body.

2. The Blood Plasma.—The plasma forms an important constituent of the inflammatory exudate. Normally passing as lymph from the capillaries into the tissues and being absorbed thence into the lymphatics, in

inflammation it is poured out in such quantity that adequate absorption is impossible. It accordingly collects in the tissues, bringing with it antibodies such as agglutinins, bacteriolysins and opsonins. The amount varies greatly depending mainly on the site of the inflammation. It is specially abundant in loose subcutaneous tissue and in serous sacs, but even in such an organ as the appendix the muscle fibers may be widely separated by inflammatory edema (Fig. 4). It is the chief cause of the swelling in inflammation, and in subcutaneous positions the edema may be recognized by the phenomenon of pitting on pressure.

Fibrin is formed as the result of the union of thrombin liberated from the shed leucocytes with fibrinogen in the plasma, and consists of an in-

Fig. 4.—Inflammatory edema in appendix. × 200.

Fig. 5.—Abundant fibrin formation. × 360.

terlacing of fine threads (Fig. 5). It is specially abundant on a serous surface such as the peritoneum or pleura, or on a mucous surface covered with stratified epithelium such as the pharynx. In the latter site it frequently binds together the necrosed epithelial cells to form a false membrane, which is firmly adherent to the surface. It is only present in small amount in deep inflammations, and is not found in an abscess where it has been digested by the proteolytic ferments of the leucocytes and bacteria.

In common with the other factors in the inflammatory process, fibrin has a useful purpose to perform. It is essentially protective and limiting. In appendicitis, for example, the fibrin endeavors to limit the process by attempting to shut off the inflamed area from the general peritoneal

cavity. If the surface of the bowel is red, intensely congested, and shows no fibrin the prognosis is much worse than when it is covered with an abundant coating of fibrin.

3. The Cells of the Tissues.—The cells of the inflammatory exudate are not derived from the blood alone. Many rise from the tissues. We may therefore distinguish two groups of cells, the one hematogenous, the other histogenous in origin.

These histogenous cells belong to the great group of the wandering cells of the body. Whilst most of the cells of the body are fixed in their position and anchored to one another, others are free and lead a wandering nomadic life until they perish. The wandering cells are concerned with the process of inflammation, the fixed cells with the process of repair. To the former class belong all the leucocytes of the blood, which are not only driven around in the blood stream, but possess the power of independent movement.

Many of the tissue cells are also free wanderers. They make their way through the interstices of the tissues by virtue of their ameboid movement, and when a living tissue is fixed instantaneously their long pseudopodia are often caught before they have time to retract. These are the cells which play an important role in the later stages of acute inflammation, and particularly in all forms of chronic inflammation.

The chief of these cells are the *histiocytes* or *macrophages*. The former name indicates their origin, the latter their appearance and function. They belong to the reticulo-endothelial system, that is to say they will take up vital dyes exposed to them. In contact with a foreign body they become grouped to form multinucleated giant cells. The so-called *lymphocytes*, or small round cells, which are so numerous in the late stage of acute inflammation and also in chronic inflammation, are largely derived from the tissues, possibly from the cells of the perivascular lymph sheaths. The *plasma cell*, probably derived from the lymphocyte, presents a very characteristic appearance. It is larger than a lymphocyte, irregular or polygonal in shape, with an eccentric nucleus showing a clock face arrangement of granules, and an abundant basophilic cytoplasm in which there may be a clear area close to the nucleus. With Pappenheim's pyronin-methyl green the cytoplasm stains bright red. It is a cell of chronic inflammation and is present in large numbers in syphilitic lesions.

The Localization of Infection.—The inflammatory reaction tends to prevent the dissemination of infection. Speaking generally, the more intense the reaction, the more likely is the infection to be localized. Staphylococci produce an acute inflammatory lesion in which the bacteria tend to remain confined to the lesion. Streptococci may have spread to a distance before a reaction manifests itself. In syphilitic infection the spirochetes may be carried throughout the body before the primary lesion develops. In addition to the element of acuteness of reaction bacteria differ in their inherent tendency to become disseminated.

Menkin has drawn attention in experimental inflammation to the importance of mechanical obstruction in limiting the spread of infection. This obstruction is due partly to the formation of a network of fibrin, partly to occlusion of the lymphatic vessels. These factors tend to cause what may be called fixation of the infective agent in the early stages

before phagocytes have time to accumulate. If iron salts are injected into the peritoneal cavity, they can soon be demonstrated in the regional lymph nodes; if an aseptic peritonitis is first produced, the iron does not reach the nodes, as the channels to the nodes are blocked. In the immunized animal, as Rich has shown experimentally, fixation is due to the action of immune bodies, which cause the bacteria to be agglutinated and held in situ.

Related to the question of the success or failure of localization is that of *absorption of bacteria and toxins* from the tissues. It might be thought that bacteria introduced into a freshly made wound would readily enter the open ends of the divided vessels, but such is not the case. McMaster and Hudack examined a freshly made wound under the microscope and observed that the blood vessels shut down within a few minutes, whilst the lymph vessels remained patent for over forty-eight hours. The experimental work of Barnes and Trueta has shown that bacteria and toxins of large molecular weight are absorbed from the tissues only by the lymphatics, and that such absorption will occur much less readily if the limb is immobilized. It is well known that no lymph will flow from an immobilized leg. Russell viper venom and tetanus toxin, with molecular weights over 20,000, are not absorbed from an immobilized limb, indicating absorption by lymphatics, whereas cobra venom (molecular weight under 5000) and strychnine are absorbed with equal rapidity from a normal limb and from one whose lymphatics are obstructed or from one that is immobilized, indicating absorption by blood vessels. In inflammatory or other edema the lymph flow, and therefore absorption, is greatly increased. This may be prevented by enclosing the injured part in a closed plaster cast, a method which Trueta has shown to be effective in the treatment of infected wounds.

CHRONIC INFLAMMATION

Inflammation is usually divided into acute and chronic forms. For clinical purposes this is convenient, but from the pathological point of view these are but two phases of the same process. Acute inflammation is due to the action of an acute irritant, is marked clinically by heat, redness and swelling, and pathologically by hyperemia and exudation. Chronic inflammation is due to the action of a chronic irritant, there is no heat or redness, although swelling may be present, and the pathological feature is the abundant formation of new tissue. The polymorphonuclear is the cell characteristic of acute inflammation, for the reason that in the acute condition phagocytosis seems to be an important factor in defense. The lymphocyte, endothelial cell, and plasma cell form the bulk of the inflammatory cells in the chronic form, although the exact part which they play is as yet uncertain.

Chronic inflammation may be the *sequel to an acute attack* or may be chronic from the beginning. After an acute attack the irritant may not be completely removed and may remain to produce a chronic inflammation. An acute osteomyelitis may leave behind an infected sequestrum which produces such a degree of chronic inflammation that the bone becomes greatly thickened. We must not confuse with this condition the much commoner one of fibrosis and thickening due to a previous acute

inflammation. The appendix thickened from previous acute attacks is not an example of chronic appendicitis. A thickened pleura is not necessarily the site of a chronic pleurisy.

The inflammation may be *chronic from the beginning.* A nonbacterial irritant such as a foreign body may act in this way. Pyogenic bacteria do not act thus, but certain slow-acting bacteria, of which tuberculosis, syphilis, actinomycosis and leprosy are the most important, produce a slow inflammatory reaction marked by accumulation of lymphocytes and macrophages together with a marked proliferation of fibroblasts. There is thus the formation of an abundant granulation tissue, at first cellular, but later becoming fibrosed. For this reason these conditions are grouped together as the infectious granulomata.

III. REPAIR

Inflammation is in its essence a struggle between two forces representing destruction and conservation. In every case these two processes are present. The end result depends on which proves the stronger, and upon the degree of destruction produced before repair sets in. To every case there are three possible terminations: (1) resolution, (2) suppuration with tissue death, and (3) repair with fibrosis.

Repair is sometimes spoken of as a part of inflammation. This we cannot but feel is a mistake. It is true that the two processes are most intimately blended, and it is convenient to consider them both at the same time, but that does not mean that they are one and the same thing. MacCallum compares inflammation to a fire in which, while the flames are still burning fiercely in one part of the building and the fire engines are pouring on floods of water, gangs of carpenters have already begun to arrive, and are busy with reconstructive work on the burnt out portions. The two processes go on side by side, but they are quite independent of one another, and either may be absent. We have already seen that the cells concerned are also different; in inflammation it is the wandering cells, in repair the fixed cells of the tissues which are concerned.

Although inflammation becomes more complex and probably more efficient as we ascend the animal scale, the reverse is true of healing. The latter becomes more complete the lower down we go, and in the lowest forms of life not only entire organs or parts may be replaced, but a complete new individual may be formed. The experiments of the Abbé Spallanzani in 1768 in this respect are classical. Working on the earthworm he was able to obtain a new head five times in one animal. In man it is useless to look for the restoration of organs or parts. All that can be hoped for is a regeneration of tissues, and even this is limited in extent, and by no means shared by all the tissues. It is one of the penalties we have to pay for our aristocratic position in the animal hierarchy.

Moreover there is an aristocracy of tissue as well as of species. The more highly developed the tissue, the less power has it of regeneration. Comparatively lowly specialized tissues such as connective tissue, the periosteum, or the epidermis are readily regenerated. Highly specialized cells such as those of the heart or the central nervous system are not capable of regeneration. The difference is nicely seen in the case of a secreting gland, in which the somewhat plebeian cubical epithelium of

the duct can be reformed in a manner which is impossible for the more specialized columnar epithelium of the acinus.

The difference between the aristocratic and the plebeian tissues has been forcibly expressed by John McCrae. "The parenchymatous cell," he says, "is the professional man in a community, specially trained, not to be replaced but by one of his own class, impressionable by even slight external stimuli, not prone to be physically hardy, not overgiven to reproduction. The supporting cell, on the other hand, is its laboring-class brother, not trained in any highly special task, whose supportive work can be replaced by any kind of tissue, even scar tissue, not readily impressionable even by powerful external stimuli, physically strong, and ready in reproduction. These two cells lie side by side in the kidney, exposed to the same toxic influences, but reacting to them each in its own way. A toxin strong enough seriously to damage the high-class cell is only strong enough to irritate the low-class cell to reproduction. When the high-class cell is killed by toxin, in the absence of regeneration by the remaining tubular cells, it leaves no one of its kind in its stead, and its place is occupied, but its function is not performed, by the progeny of its laboring-class brother."

The process of repair is so commonplace that it excites no wonder, and yet it is one of the most mysterious in biology. Fibroblasts which have been quiescent for years spring to life and proliferate actively in the course of a day or two. Putting aside such vague conceptions as the disturbance of tissue tension, it seems safe to say that the stimulus which rouses the cells to grow must be a chemical one. Hammett has shown that in the nuclei of dividing cells, both animal and vegetable, there is a rearrangement of sulphur in the molecules. The sulphhydryl group -SH is present in all actively dividing tissue and appears to form its most characteristic feature. The work of Reimann demonstrates the remarkable stimulating effect which sulphhydryl has upon the healing of wounds, so that it would appear that it was a kind of "wound hormone."

The process of repair may conveniently be studied in two classes of cases: (1) healing of a wound with loss of substance, and (2) healing of an incised wound in which the edges are brought together without loss of substance. Although it is convenient to study the process in the case of a wound, it may be seen in any inflammation which goes on to recovery. Adhesions shutting off an inflamed appendix from the general peritoneal cavity, the zone of fibrous tissue which walls off a chronic cerebral abscess, the omentum overlying and adherent to a gastric ulcer which threatens to perforate, are examples of a general tendency to repair as much as the healing of a wound made by the surgeon's knife.

1. Healing of a Wound with Loss of Substance.—A clean aseptic wound with loss of substance is in the same condition as a healthy or healing ulcer, and the same changes occur in both. The gap in the surface is filled with various elements of the inflammatory exudate, chiefly coagulated plasma, bound together by interlacing strands of fibrin. The capillaries at the sides and base put forth solid buds of endothelium which grow into the mass, unite with one another, and become canalized and filled with blood, thus forming a network of new capillaries (Fig. 6). In this way the exudate becomes vascularized and the fibrin, which at first forms a scaf-

folding for this new formation, becomes absorbed before the new capillary loops.

At the same time the connective tissue cells proliferate, and develop into plump fusiform cells with vesicular nuclei and branching processes called fibroblasts (Fig. 7). This fibroblastic proliferation is the most striking feature of the process of repair. In the embryo the fibroblasts form an actively growing tissue, but in the adult they are in a resting condition, for they need for their multiplication substances which are not present in the lymph and blood streams. When grown in embryonic juice they again become active, and Carrel has succeeded in maintaining this activity for a period of fifteen years. This embryonic activity is also resumed in inflammatory tissue, for the fibroblasts can now feed on the substances liberated by the degenerating leucocytes and macrophages.

The fibroblasts support the capillaries and permeate the fibrin, forming an interlacing network throughout it. Bunting and Eades have shown that the fibroblasts show a certain degree of polarity which may be altered by mechanical torsion. In very young healing tissue the fibroblasts are at first parallel to the sprouting vessels and perpendicular to the surface. Deeper down (the tissue being older) they are oblique. In the depths of the wound they are parallel to the surface and therefore perpendicular to the vessels, as in the final scar. The same change is observed in an organizing pericardial exudate, but if adhesions are formed the fibroblasts are found to maintain their original position parallel to the vessels. Bunting and Eades produced mechanical torsion in healing experimental wounds in animals and found that in this way they were able to alter the polarity of the fibroblasts, the direction of these cells being dependent on the line of torsion.

Fig. 7.—Fibroblasts and new capillaries in granulation tissue. × 350.

Owing to the prolific growth of this new vascular tissue the floor of the gap becomes covered with little, translucent, rosy, nodular masses or granulations which rapidly fill in the gap, give the floor a velvety appearance, and bleed readily on account of their great vascularity. This new formation is called *granulation tissue*. It is best seen on a healing surface, and its presence indicates that healing is taking place. Such vascular connective tissue may be found in any organ, and beautiful examples are seen in inflammation of the appendix, Fallopian tubes, etc. Wherever it occurs it is called granulation tissue.

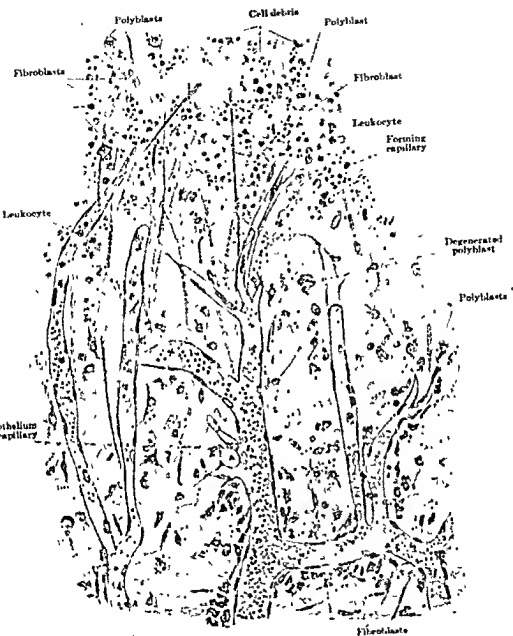The fibroblasts lay down fine connective tissue fibers between the

Fig. 6.—Developing vascular tissue. Growth is proceeding from below upward (Maximow).

cells. These fibers increase in number and thickness until definite fibrous tissue can be recognized, and the originally cellular granulation tissue becomes gradually fibrosed. The fibroblasts are compressed between the bundles of new fibers, until they appear only as thin connective tissue cells consisting of little more than an elongated nucleus. The capillaries become obliterated, so that the vascular granulation tissue finally becomes a fibrous non-vascular mass of *scar tissue.*

The history of the healing of a wound is the history of surgery. A few extracts from Samuel D. Gross's "Elements of Pathological Anatomy," published in 1839, may be of interest to the historically-minded. "The process of granulation is one of the grand operations employed by nature for the cure of wounds and the filling up of ulcers. A granulation is a small, vascular body, generally somewhat mammilated in shape, more or less red, sensitive, and capable of secreting pus. The vascularity of these little bodies is much greater, I am disposed to think, than is generally imagined. That they are liberally supplied with vessels is at once indicated by their florid complexion, by the astonishing rapidity of their growth, by the facility with which they bleed when touched, and by the fact that they become hard and tumid if filled with injecting matter. Cicatrization is the process which nature employs to heal wounds and ulcers. It is the finishing stroke, if the expression be allowable, of granulation—the labor which is necessary to polish the surface of the sore, to contract its diameter, and to bring it as nearly as possible to a level with the surrounding structures. At first the cicatrix is extremely vascular, soft and of a bluish color; afterwards the vessels decrease in size and number, and the part becomes dense, bloodless, and whiter than the original skin. In most instances the reproduction is imperfect. This is the case even with the skin. The cutis is never so strong or so capable of resisting the effects of disease as in the normal state; its inner surface is not reticulated, nor is it provided with sebaceous follicles. No hairs are to be seen in the scar; for their roots having been destroyed, they cannot, of course, be reproduced. The same imperfect development is observed in the cicatrization of the mucous or some other tissues." A hundred years have detracted little or nothing from the accuracy of these observations.

The method of secondary healing or healing by granulation tissue is by no means confined to the filling of a gap on the surface. It is the means whereby any cavity in the tissues becomes filled, although the attempt is not always successful. The cavity is occupied by blood or an inflammatory exudate, which is gradually replaced by granulation tissue. Even an abscess cavity is filled up in this way after the pus has been allowed to escape. A cavity in bone containing blood may fail to be obliterated, owing to the comparatively non-vascular character of the tissue, and for years may remain in this condition, full of fluid autolyzed blood, and a constant menace to the patient from the danger of infection supervening.

The *epithelium* at the edge of the wound or ulcer soon shows signs of proliferation, and a thin bluish-white line appears, which spreads inwards covering the surface with a layer of young epithelial cells, much in the same way as the first filaments of ice extend over a pond on an autumn evening. Should some factor such as chronic infection prevent the epithe-

lium from covering the raw surface it may send long processes down into the cutis vera giving a picture which may closely resemble an early carcinoma (Fig. 8). Indeed such chronic ulcers may form the starting point of a malignant growth. When scar tissue has formed, the surface epithelium is white, bloodless, slightly wrinkled, and depressed below the surface from contraction of the scar.

A granulating surface presents a most efficient barrier against bacterial invasion. It is, however, easily injured, for the granulations are delicate, and the young epithelial cells struggling to gain a footing on the

Fig. 8.—Chronic ulcer in which healing has been interfered with. Long down growth of epithelium into deeper tissue.

new surface are easily dislodged. The interfering and too vigorous swab, the over frequent change of dressings, the stream of strong antiseptic may do more harm than good. Free drainage should be provided for the escape of any discharge, and the granulating surface should be protected, but nothing should be done to interfere with that remarkable tendency to heal which is present in all healthy tissue.

2. **Healing under a Crust.**—This is merely a modification of secondary healing. If there has been a good deal of hemorrhage a blood clot will form on the surface, which, if allowed to remain, will act as a protective covering under which healing will proceed quietly and unobtrusively. The

same is true for the scab or crust which forms when the discharge from the surface of the wound is allowed to dry. This crust subserves the three-fold function of a protection, a scaffolding for the support of the young connective tissue, and a source of nourishment for the same. The distinguishing feature of this form of healing is that the new epithelium extends over the surface under cover of the crust, so that when the latter drops off the raw surface is completely covered. Although there is plenty of granulation tissue under the epithelium, the patient escapes the discomfort of a raw granulating surface.

3. **Healing of a clean incised wound with no loss of tissue.** Here there is no granulating surface, and yet the young vascular connective tissue which we have already recognized as granulation tissue forms the principal feature. Into the slit-like gap made by the knife blood plasma and

Fig. 9.—Healing of incised wound. A, Three hours: there is exudate on right wall of incision. × 33. B, Seven days: edges sewed together by fibroblasts and surface covered by epithelium. × 33.

whole blood are poured, which on clotting furnish the fibrin network that forms the scaffolding for the repair builders. Once more the capillary loops and young fibroblasts first use and then replace the scaffold, the capillaries absorbing any débris to be removed, and the fibroblasts "sewing together" the opposing surfaces (Fig. 9).

The time required for complete repair will depend on a number of factors, of which the amount of tissue destruction and the degree of asepsis are the most important. The presence of bacteria will retard and may completely prevent the process. It is evident that it is impossible to give an estimate of the time required for a wound with loss of substance to heal, but the following table will give an indication of the approximate times of the various stages of the healing process in the case of an incised wound.

HEALING OF AN INCISED WOUND

End of 12 hours: Vascular and connective tissue reaction begins.
End of 2nd day: Granulation tissue appears.
End of 4th day: Temporary clot replaced by granulation tissue.
End of 5th day: Epithelium covers narrow wound. Definite fibrils appear.
End of 3 weeks: Dense non-vascular scar tissue is formed.

The exact age of a wound may be very important in medicolegal cases, but great caution must be exercised in expressing an opinion, for the individual tendency to heal varies much. Even clean-cut surgical wounds may show delay, so that several days later there may be little evidence of repair, and this is far more true of healing by granulation tissue.

The process of repair with formation of granulation tissue and subsequent fibrosis may occur in any inflamed organ in which the process has passed the stage where resolution is possible, that is to say where there is tissue death and thrombosis of the vessel. The presence of fibrin in abundance appears to act as a stimulant to the formation of granulation tissue, possibly providing the cells of that tissue with nourishment. The formation of granulation tissue with fibrosis and consequent adhesions is therefore a prominent feature in inflammation of serous surfaces such as the pleura, pericardium and peritoneum.

Defective Wound Healing.—Healing is the most fundamental process in surgery. The effective and rapid formation of collagen is the essential process in scar formation. It has long been recognized that local factors such as the amount of damaged tissue and exudate, the character of the vascular supply, foreign particles and infection will interfere with healing. It is known that Vitamin C deficiency will interfere with collagen formation. In guinea pigs, which are especially susceptible to scurvy, a sub-scorbutic diet at once leads to delayed healing and poor scar formation. In man the same thing happens, but the deficiency period required is long. In self-inflicted wounds when on a Vitamin C deficient diet Lund and Crandon found that healing was interfered with when the diet was continued for 6 months, although it was normal at the end of 3 months. Healing became normal as soon as ascorbic acid was given. Many hospital patients with long-standing gastro-intestinal disorders are low in Vitamin C, and in such persons healing is apt to be poor and the wound may break down.

THE COURSE AND VARIETIES OF INFLAMMATION

Although for descriptive purposes it is convenient to consider inflammation in a typical case, yet it must be borne in mind that there is no process which varies more in its course, its intensity, and its results. Of the main features of inflammation now one, now another may be emphasized, so that the picture may present the changing colors of the kaleidoscope, yet all are but variants of one process. The variations depend partly on the organ affected, but more on the relative strength of the attacking and defensive forces. We have already seen that there are three possible courses which may be followed, namely resolution, suppuration with tissue death, and repair with fibrosis. These will now be considered somewhat more in detail.

1. **Resolution.**—Up to a certain point inflammation may be completely recovered from, in which case resolution is said to have occurred. When bacteria invade the wall of the appendix the irritation calls forth the usual vascular changes and inflammatory exudate. If, however, the attack be weak or the defense vigorous, the bacteria are devoured and removed by the phagocytes, their toxins neutralized by the serum, any fibrin formed is dissolved, the inflammatory cells re-enter the circulation, and the part returns to normal, bearing no trace of the conflict which has taken place, because there has been no actual destruction of tissue. In the same way a boil may resolve, without the formation of either pus or fibrous tissue. This, fortunately, is the usual course for inflammation to follow.

2. **Suppuration with Tissue Death.**—When the infection with virulent bacteria is intense, overwhelming the resistance, in addition to the formation of an abundant inflammatory exudate there is death of the tissue cells. Large numbers of these are killed by the bacterial toxins. Disturbance of the circulation due to thrombosis of the vessels may also play a part. At first the necrosed cells form a solid mass, but the proteolytic ferments of the numerous leucocytes soon produce liquefaction, so that the inflammatory area becomes a cavity or abscess, containing a fluid in which float living and dead leucocytes. This fluid is called pus. In such a case the part cannot return to normal, for the process of replacing the destroyed tissue will leave an indelible scar.

An abscess, then, is a cavity containing pus and surrounded by a wall of inflamed tissue. Taking as an example an abscess of the kidney, the kidney cells immediately lining the abscess cavity will be completely necrosed and disintegrated, those further out will show lesser degrees of degeneration such as cloudy swelling and fatty degeneration, and on the outskirts the cells will be healthy. Large numbers of bacteria are present in the wall.

In an abscess which has lasted for any length of time, whether or not it has been opened, a zone of granulation tissue is formed in the wall which separates the living from the dead tissue. It is remarkable for the numbers of large phagocytic cells which infiltrate its meshes. Owing to the fact that numerous pus cells or leucocytes are shed off from it, this lining is sometimes called the pyogenic membrane.

An abscess may advance, remain stationary, or recover. Should it advance, a progressive destruction of the cells occurs, so that more of the wall becomes liquefied and added to the central pus. Or it may burrow its way through the tissue, following the line of least resistance, and open on the surface. To become stationary is uncommon, but a chronic liver abscess or a pyosalpinx may become walled off by fibrous tissue, and neither advance nor recover. Finally, when the abscess has discharged on a surface or has been opened by a surgeon recovery will commence, the cavity being quickly filled by granulations springing from the surrounding walls. Even without discharging on a surface a small abscess may become invaded by granulation tissue and ultimately fibrosed, but this is not of common occurrence.

A septic or infected wound is merely a superficial abscess. The condition and behavior of the bacterial flora of such a wound may readily

be studied by the ingenious methods introduced by Sir Almroth Wright. Impression cultures may be made by applying a cover-glass to the surface of a wound and then transferring it directly to the surface of an agar plate. In this way a "bio-pyo-culture" is obtained. Such cultures revealed the interesting fact that syringing of the wound served to remove the larger formed elements—the leucocytes, but failed to remove the smaller formed elements—the bacteria. A cover-glass impression made immediately after syringing the wound shows abundant bacteria but no leucocytes, and an impression culture will show large numbers of colonies. When some hours are allowed to elapse the picture is quite different; there are now large numbers of freshly migrated leucocytes interspersed among which are a few bacteria, and when bio-pyo-cultures are made the leucocytes continue the attack and kill off the bacteria.
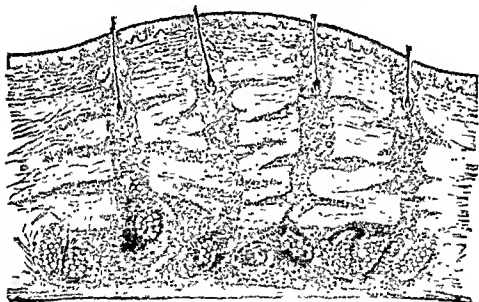
Fig. 10.—Section of a carbuncle of the back, showing infiltration of the adipose layer of the cutis vera and extension toward the surface through the columnae adiposae. (Keen's Surgery, Vol. I.)

The application of antiseptics does not influence this cycle of events. Indeed these poisons hinder the migration of the leucocytes, and form a layer of coagulated albumin over the walls of the wound which serves to confine the bacteria. It is obvious that such methods must prove of great assistance to the worker investigating the different methods of treating infected wounds.

A *boil* is an example of an abscess located in a hair follicle or a sebaceous gland, the infection having penetrated the skin through the opening of one of the ducts as the result of friction or pressure. The usual invader is the Staphylococcus aureus. Should the infection penetrate to the deeper layers of the skin and the subcutaneous fat, a *carbuncle* may be formed; this consists of a series of communicating abscesses which discharge by separate openings on the surface (Fig. 10). In both of these

cases there is a marked fibroblastic reaction which imparts a characteristic induration to the lesion.

An *ulcer* is an interruption of the continuity of a surface with accompanying inflammation (Fig. 11). The histological structure is similar to that of an abscess; there is the same purulent discharge, the granulating wall, the surrounding area of damaged cells. The pus is free to escape so that repair can take place by the growth of granulations filling the cavity, provided that the infection be overcome so that a "healthy ulcer" is produced.

A *healthy ulcer* or healing sore (Fig. 12) presents a floor covered with firm, pinkish-red, translucent granulations, covered with a slight serous exudation in which are a few pus cells. The edge is sloping and is bordered by a thin, bluish-white layer of young ingrowing epithelium. The surrounding parts are normal, apart from a slight degree of hyperemia.

Fig. 11.—Acute ulcer showing sudden break in epithelium and abundant inflammatory tissue. × 75.

An ulcer may remain un*healthy* owing to unfavorable local or general conditions, of which bacterial infection and defective circulation are the most important.

When the virulent bacteria are still present there is no attempt at repair, the base of the ulcer has an angry appearance and is bathed with thin yellow pus, the edges are ragged and irregular due to tissue destruction still going on, the discharge is profuse and offensive, and the surrounding parts are hot, red and edematous.

When defective circulation is the important factor, as in the ulcer on the lower third of the leg often associated with varicose veins, the base is covered with soft, edematous, unhealthy-looking granulations (popularly known as "proud flesh"), the edges become sclerosed from formation of the fibrous tissue, and the epithelium shows no sign of ingrowth. This form of ulcer (ulcus cruris) is due to the tissues becoming

water-logged, as a result of which their resistance to infection and trauma becomes greatly impaired, so that necrosis of the surface readily occurs. The ulcer will not heal until the circulatory disturbance has been rectified. It is a mistake to call these ulcers "varicose" because they may be due to other disturbances of the vascular balance of a limb than varicose veins. Repeated pregnancies, with the production of "white leg," phlebitis and thrombosis may be a factor, as may be phlebosclerosis, a fibrosis of the walls of the veins in which the thickened vessels can be felt. Compression by elastic bandage and, if necessary, the injection of varicose veins, works wonders with the ulcer.

The *tuberculous ulcer* (Fig. 12) is seen typically in the neck in cases of discharging tuberculous glands. The base is pale and ragged, and often covered with gray sloughs, the edges are bluish in color, thinned out and undermined so that a probe may be passed for some distance underneath
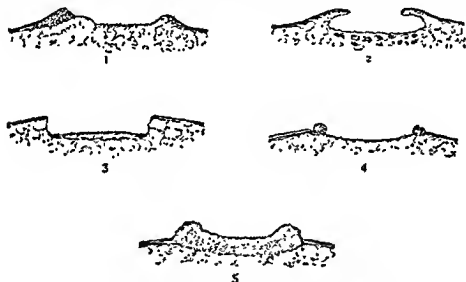
Fig. 12.—Varieties of ulcers: 1, Simple healing ulcer; 2, tuberculous ulcer; 3, syphilitic ulcer; 4, rodent ulcer; 5, epitheliomatous ulcer. (After Rutherford Morison.)

them. *The discharge is thin and watery, and contains shreds of necrosed* tissue.

The *syphilitic ulcer* (Fig. 12) presents a characteristic sharp, punched out appearance, with a base like dirty wash-leather, and an outline that is often serpiginous. The edges are raised and indurated, and the discharge thick, glairy, and offensive. A common situation for such ulcers is the upper third of the leg.

The *chronic undermining ulcer* due to anaerobic bacteria is described on page 28.

A *sinus* is a tubular ulcer, which refuses to heal, owing usually to the presence of dead tissue. It is lined by granulation tissue. Many persistent sinuses prove to be tuberculous.

A *fistula* is a similar passage connecting a skin with a mucous surface or one mucous surface with another, caused by an abscess discharging by separate openings on these two surfaces.

Pus is a yellow material with an alkaline reaction, consisting of leucocytes living and dead, mainly polymorphonuclears, although lymphocytes and macrophages may also be present and occasionally necrosed tissue cells. It usually contains living bacteria, but in such a condition as a pyosalpinx of long standing or a chronic abscess of the brain or of bone it may be sterile owing to the infecting bacteria having died out. Its physical characters differ somewhat with the infecting organism and the site of the infection. Pus cells in a gonorrheal discharge are well preserved, those in an empyema are much disintegrated, the difference being due to the difference in age of the exudate. The pus in staphylococcal infection is creamy in consistence and has a mawkish odor, that in streptococcal infection is sero-fibrinous in consistence and without odor. Tuberculous pus is flaky, that due to B. pyocyaneus has a greenish or blue color from the pigment pyocyanin, that of a brain abscess has also often got a green tinge, perhaps for the same reason, whilst the pus of B. coli infection has a characteristic fecal odor.

Septicemia and Pyemia.—The products of bacterial action may be absorbed into the blood, giving rise to sapremia, or the bacteria themselves may enter the stream, a condition of septicemia.

Sapremia is a condition of intoxication due to the action of saprophytic bacteria. These are unable to invade the living tissue, but flourish in dead tissue such as occurs in a wound with extensive laceration of the soft parts or in the remains of a placenta retained in the uterus. Owing to the great proteolytic power of the saprophytes the proteins are decomposed into toxic products, which when absorbed produce symptoms of intoxication. When the toxin factory is destroyed, as by scraping out the uterus or "débridement" of a wound, the symptoms rapidly subside.

Septicemia is a term familiar to everyone, and yet when we analyze it we find it difficult to define. Strictly speaking, any condition in which micro-organisms circulate in the blood is a septicemia. In a bacteriological sense this is true. In a clinical sense it is certainly not true. We must distinguish between a bacteremia and a septicemia. Bacteria probably enter the blood in every infection, but they are speedily destroyed and are therefore not found in blood culture. Moreover it is not only in infections that bacteria circulate in the blood stream. When a boy receives a blow on the shin and as a result develops acute osteomyelitis of the tibia, the infection is admittedly a hematogenous one, and the circulating blood must therefore have contained bacteria at the time of the injury. Such a person is suffering from a bacteremia but not a septicemia. The difficulty is best solved by using septicemia as a clinical not a pathological term; it indicates a condition characterized not only by the presence of bacteria in the blood, but also by the development of certain clinical manifestations (pyrexia, petechial hemorrhages, etc.) suggesting the presence of these bacteria. The number of the circulating bacteria, as shown by plating blood cultures, may remain stationary, or may increase or decrease. The prognosis may well be based on such blood culture observations. It is commonly stated that an increase in the circulating bacteria is due to multiplication in the blood stream. This is open to doubt, and in any case it is very difficult to prove. It

appears more probable that it is due to the entrance of fresh bacteria from the original focus. Into every case of septicemia there should enter the conception of some local focus of infection, often undiscovered, from which, as a result of a breaking down of the protective barrier between bacteria and host, organisms enter and continue to enter the blood stream. When the source of supply is removed, the bacteria soon disappear from the blood.

Pyemia is characterized by the appearance of secondary foci of suppuration in various parts of the body. It is seldom that such secondary foci are caused merely by a settling down of the circulating bacteria. They are caused rather by the lodgment of septic emboli formed as the result of a breaking-up of an infected embolus or a septic vegetation on an inflamed heart valve. Thrombo-phlebitis, in the uterus or elsewhere, is the commonest cause of pyemia. The chills characteristic of the condition are due to the periodic flooding of the circulation with bacteria and breaking down proteins.

The common sites for the formation of a septic thrombus are the middle ear, with infection of the lateral sinus and the formation of abscesses in the lung and later in the viscera generally, the appendix with secondary abscesses in the liver (Fig. 13), the uterine veins in puerperal sepsis, and the hemorrhoidal veins. After the formation of pyemic foci in the organs has been established, the joints are liable to become infected, the inflammation varying from a mild arthritis to complete *destruction of the joint*.

Fig. 13.—Portal pyemia; abscesses of the liver secondary to suppuration in the appendix. (After Rutherford Morison.)

The clinical signs of septic thrombosis with pyemia are very characteristic, namely, a series of severe rigors accompanied by marked fever occurring about every 24 hours, the patient feeling comparatively well in the interval. When the primary focus of infection is removed or cut off from the general circulation it is remarkable how quickly recovery may set in, even though secondary abscesses have been formed. The best example is the effect of tying the internal jugular vein in septic thrombosis of the lateral sinus.

The *post-mortem appearances* in septicemia and pyemia are characteristic. In septicemia there may be marked decomposition, and rigor mortis is but little marked. Petechial hemorrhages are present in the pleura, pericardium, and endocardium. The blood is fluid and dark. The spleen is enlarged, soft and friable. The muscles and the heart are friable and stained red. The lining of the blood vessels is similarly stained
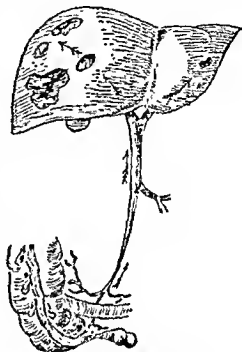
owing to decomposition of the red blood cells. In pyemia, in addition to the above findings, small embolic abscesses may be present in the lungs, heart, kidney, liver, and other organs. These abscesses lie mostly just under the surface of the organ. The pleural and pericardial cavities may contain pus due to spread of infection from these abscesses.

Anaerobic Streptococcal Infections of the Skin.—The work of Meleney has drawn attention to the importance of anaerobic streptococci as an occasional cause of severe skin lesions. Two of these are chronic undermining ulcer and infectious gangrene.

Chronic undermining ulcer is a rare lesion of the abdominal wall, groin, or perineum. The infection starts in an operation wound in the intestinal or genital tract, or in an accidental wound. Healing fails to occur in the usual time, and the skin margins are slowly undermined with liquefaction of the subcutaneous fat and connective tissue; there is no gangrene. Secondary openings are formed, whilst bridges of skin are left. Pain may be excruciating. *No real idea of the clinical condition can be got from this cold account;* one has to see a case to appreciate the terrible, remorseless character of the lesion. The lesion is caused by micro-aerophilic *hemolytic* streptococci, *i. e.*, streptococci which grow in the presence of only a small amount of oxygen and which are demonstrated by anaerobic culture. The process can best be controlled, therefore, by means of slowly acting oxidizing agents such as zinc peroxide. The course is marked by *fever and prostration,* terminating unless treated properly in death, not infrequently from suicide.

Infectious gangrene of the skin and subcutaneous tissues has been descriptively named by Meleney: *post-operative progressive bacterial synergistic gangrene.* The lesion is also called a *symbiotic ulcer.* It is a chronic gangrene, generally following drainage of a peritoneal abscess. There is very little general reaction, but the whole region becomes exquisitely tender, and the patient is worn down by pain and discouragement. The early lesion presents a purplish center and a brilliant red outer zone. The center undergoes necrosis and becomes undermined and finally separated with the formation of an ulcer. The infection spreads remorselessly in the subcutaneous tissue, and the area of gangrene and ulceration becomes ever larger. The condition is a manifestation of bacterial synergism or symbiosis, the two organisms being a micro-aerophilic *nonhemolytic* streptococcus and a hemolytic *Staphylococcus aureus.* The streptococcus probably comes from the intestinal tract, the staphylococcus from the skin. When either of these organisms is injected separately into an animal no lesion is produced, but when they are combined gangrene results. Treatment is wide excision and the use of an oxidizing agent (zinc peroxide).

3. Repair with Fibrosis.—The process of repair has already been studied. Its most important clinical feature is the formation of fibrous tissue with consequent thickening and contraction. The mechanical effects depend upon the site.

In the skin there will be a scar, always a point of weakness. In serous membranes such as the pleura and peritoneum there will be adhesions, which may or may not cause subsequent trouble. A personal factor has to be reckoned with in certain cases, for in some patients adhesions appear

to form with much less provocation than in others. A tube will be stenosed, the nature of the functional disturbance depending upon the organ involved. Thus in the urethra or ureter there may be hydronephrosis, in the Fallopian tube or epididymis sterility, in the bile duct distension of the gall bladder, in the appendix repeated attacks of inflammation from narrowing of the outlet, in the esophagus difficulty in swallowing. Cysts may be formed, in the breast from obstruction to the lactiferous ducts, in the ovary from sclerosis preventing dehiscence of the follicles.

The three main courses of inflammation have been considered, but the varieties are endless, depending partly on the nature and virulence of the irritant, partly on the tissue involved.

A *purulent* inflammation is one in which suppuration with formation of pus is the prominent feature.

Should fibrin formation be marked, as in inflammation of serous membranes such as the pleura and peritoneum, the inflammation is called *fibrinous*.

The term *catarrh* is applied to a mild inflammation of a mucous membrane in which the irritant acts as a stimulant to the mucous cells. These pour out an abundant secretion of mucus which mingles with the serum of the inflammatory exudate to form a thin watery or sticky discharge containing a varying number of leucocytes and desquamated epithelial cells. Examples of catarrh may be found in any mucous membrane, for instance cold in the head, bronchitis, gastritis, mucous colitis, catarrhal appendicitis. When the injury is greater there is death of the cells, and a more abundant inflammatory exudate, so that the condition becomes purulent.

Finally in very severe inflammation of a mucous membrane there may be great necrosis of cells, and when these are bound together by fibrin into a membrane adherent to the surface the inflammation is called *membranous* or *diphtheritic*. The best example is provided by diphtheria, but other severe irritants such for instance as steam, may produce a similar condition in the throat.

It is possible to multiply almost ad infinitum the different varieties of inflammation, giving each a name, but to do so is merely to cloud counsel, for in every case the basic changes are the same, resolution, suppuration, or repair with fibrosis, as the theme, in Adami's happy phrase, runs in a piece of music all but hidden under variations.

WOUND INFECTION

Infection of a wound by bacteria is injurious for two reasons: (1) it delays healing of the wound; (2) the infection itself may prove dangerous or fatal. The infection may be present from the beginning, bacteria being introduced at the time the wound is inflicted, or it may develop later in a wound which was originally clean. The infecting bacteria may be aerobic or anaerobic, a fundamental distinction. The anaerobes are likely to be introduced into the wound at the moment it was inflicted, but the aerobes are likely to gain access to it at some later date unless they are prevented from doing so. This fact is of great importance in relation to war wounds.

Three great advances have been made in recent years with regard to wound infection. (1) A detailed study has been conducted not only of the various kinds of organisms but more especially of the particular strains involved and the source of these strains. (2) The demonstration of the value of immobilization of the part combined with the sealed wound method originally introduced by French army surgeons in the first world war, perfected in America by Winnett Orr, and practised on a large scale in the Spanish civil war by Trueta and others. (3) The use of the sulphonamide drugs for the prevention and control of wound infection. Only the first of these will be considered here.

Aerobic Infections.—Any number of aerobic bacteria may gain access to a wound, but only two are of outstanding importance as pathogens. These are a particular type of streptococcus and a particular type of staphylococcus. Other organisms such as B. coli, B. proteus and B. pyocyaneus may infect wounds and interfere with healing. B. diphtheriae in rare cases may cause membrane formation, and micro-aerophilic cocci may produce the spreading and undermining lesions described by Meleney, but these are all exceptional occurrences.

Streptococci infecting wounds are almost without exception beta hemolytic and members of Group A in Lancefield's classification. They can be classed as Streptococcus pyogenes, and are similar to the organisms causing scarlet fever, tonsillitis, erysipelas and puerperal fever. It is the organism most to be feared in wound infections because of its great invasiveness, especially if it gains access to the wound before the defense reaction has begun. In the first world war 70 per cent of the deaths from wounds were due to Streptococcus hemolyticus infection. If the infection occurs after granulation tissue has formed there may be no clinical signs, but it delays healing, and the organisms may invade the tissues if there is subsequent surgical interference. Invasiveness may be related to the power of hemolytic streptococci to form fibrinolysin, which breaks down the defensive barrier of fibrin. Trauma and surgical roughness may also damage this barrier. Streptococci are most commonly found in infections of large abrased surfaces, and the same is true of burns.

There are two important *sources of infection:* (1) the nasopharynx of carriers who come in contact with the wound, (2) pyogenic infections and infected wounds of other patients in a hospital ward. Group A streptococci are not present in even the dirtiest wound immediately after it has been inflicted. With each succeeding day or week the danger becomes greater. *Thus in the first world war 15 per cent of wounds at the Casualty Clearing Station* (about twelve hours later) were infected. 23 per cent when the casualties reached the Base Hospital, and at the end of seven days the proportion had reached 90 per cent. Hare and Willits were unable to isolate pathogenic hemolytic streptococci from any of 355 wounds inflicted in civil life in Toronto when examined within 2 hours. Similarly with burns, 11 per cent were infected on admission to a Base Hospital, and 66 per cent were infected on the sixth day. This suggests, as Hare points out, that the infecting organisms have been added by the attendants each time the dressings are changed and the wound exposed. About 7 per cent of healthy persons are nasopharyngeal carriers of Group A streptococci. Carriers may infect a wound by talking,

coughing or sneezing, or the bacteria may be on his hands and clothes. Along the line of communications the carrier is the chief danger, whilst in hospital there is the double danger of the carrier and other infected wounds. Hospital bedding may become heavily infected, and it can be shown that violent bed-making disseminates far more germs than quiet bed-making. The sweeping of hospital floors is another method of spread of infection.

Staphylococci are common agents of wound infection, but again a sharp distinction must be drawn between pathogenic and non-pathogenic organisms. The pyogenic members of the Staphylococcus aureus group can be recognized by their property of producing coagulase, which coagulates blood serum in the test tube. Staphylococcus pyogenes aureus is less invasive than streptococci, but it may set up subacute pyemia or even fulminating septicemia. The face and bones are dangerous sites of infection, owing to the tendency to septic thrombophlebitis. Common sources of infection are the skin of carriers (surgeons, nurses, etc.) and suppurating wounds in hospital wards. Skin carriers are dangerous as the organisms cannot be eliminated by scrubbing, for they live in the ducts of the sweat and sebaceous glands, and reach the surface in the course of a long operation. They may then escape through tiny punctures in the gloves and infect the operative wound.

Anaerobic Infections.—The two important classes of anaerobic infections are gas gangrene and tetanus, both produced by spore-forming anaerobic bacilli or clostridia.

Gas gangrene is a clinical entity but not a specific disease, for it may be due to a variety of organisms. Its cause is a particular opportunity rather than a particular infection. The opportunity is a deep lacerated wound involving muscle. The three chief bacteria responsible are Clostridium welchii, which was responsible for 70 to 80 per cent of the cases in the first world war, Cl. septique (Cl. of malignant edema, Vibrion septique), producing 15 to 30 per cent of cases, and Cl. oedematiens, producing 5 to 20 per cent of cases. These are fecal bacteria occurring in contaminated soil. In addition to these *saccharolytic* gas-forming anaerobes which thrive on sugar-rich media there are *proteolytic* anaerobes which are responsible for putrefaction and liquefaction in the end stages of gangrene. The chief members of this group are Cl. sporogenes, Cl. histolyticum, and Cl. putrificum. The saccharolytic anaerobes flourish on damaged muscle and the proteolytic anaerobes on dead muscle. This fact forms the basis of treatment by débridement, or removal of injured and dead muscle.

Although gas gangrene may occur in civil and in operative wounds, particularly amputations in patients with diabetes and arteriosclerosis, it is in severely traumatized war wounds that anaerobes find the most favorable conditions. Cocci and bacilli generally enter the wound along with the anaerobes and prepare the tissues by damaging them. At the same time they lower the oxidation-reduction potential in the tissues. Moreover soil, which is a frequent contaminant of these wounds, even when sterile has the power of activating spores, probably because of the ionizable calcium salts which it contains. Muscle is highly vulnerable to anaerobic infection, provided it is first damaged. Even a slight injury

may interfere with the blood supply to a single muscle segment, and this offers a medium rich in carbohydrates and therefore suitable for the growth of saccharolytic bacteria. Gas is produced from the muscle sugar, and the gas, together with the infection, spreads along the muscle fibers with remarkable speed, separating the fibers from their blood supply. The infection is generally well ahead of the area which seems to be clinically affected. The dead muscle now provides an ideal medium for the proteolytic anaerobes, and the proteolysis results in putrefaction and liquefaction. Gas formation is therefore often but not necessarily associated with these latter changes.

The gross appearance of the wound is characteristic. The muscle is at first swollen, pale, and inelastic. Soon the color changes to brownish red, gas bubbles appear, and the consistence becomes putty-like. When putrefaction is added to gas formation the tissues become green or black, and the part crackles on palpation. Around the patient there is a graveyard smell, the smell of a corpse.

Tetanus, caused by Cl. tetani, is an infection par excellence of deep penetrating wounds, but it may follow a trivial puncture. It is a terrible complication of both civil and war wounds, but in the latter it is no longer so important as formerly on account of efficient inoculation by toxoid and the prophylactic use of antitoxin during the long incubation period between receipt of the wound and the development of symptoms. Tetanus is considered in more detail on page 72.

BURNS

Burns offer a special example of inflammation produced by an intense irritant acting over a short space of time. At first the inflammation is non-bacterial in origin, but within a space of from 12 to 24 hours cultures of the tissues involved show the presence of hemolytic streptococci in many of the mild cases and in 100 per cent of the severe ones (Aldrich). Much of the value of those forms of treatment which consist in the formation of a protective eschar over the burned surface lies in the exclusion of infection. The Chinese employed this principle 5000 years ago when they introduced the use of tannic acid in the form of tea.

The effects of a burn depend on two quite different factors: (1) its severity, and (2) its extent. An extensive burn of moderate severity may be as serious as a severe but localized burn. There are four grades of severity, commonly called degrees. The *first degree* burn is marked by hyperemia. This is the usual inflammatory type, and if sections are examined a mild exudate of serum and of leucocytes will be found. The *second degree* burn is marked by vesication. Owing to the greater irritation a larger amount of fluid is poured out, and this collects under the injured epithelium and raises it to form vesicles. The *third degree* burn is marked by necrosis of the whole thickness of skin. An eschar is formed which sloughs off, leaving an ulcer; this heals slowly with fibrosis and marked scarring. In the *fourth degree* burn the tissue is blackened and charred for a varying depth. A simpler classification is that suggested by the National Research Council of Canada (Fig. 14), in which the first degree indicates damage to the epidermis with hyperemia and vesication, the second degree involves dermis as well as epidermis with varying

degrees of damage to sebaceous and sweat glands and hair follicles, whilst in the third degree the entire thickness of the skin is destroyed.

The *systemic effects* of severe burns are very important, and there is much difference of opinion as to their explanation. When the burn covers a large surface the patient may die within twenty-four hours of shock—at least the symptoms are the same as those of traumatic shock. If death does not take place within that period a series of apparently *toxic symptoms* develop, such as delirium, vomiting, bloody diarrhea and circulatory failure. In experimental burns immediate removal of the burnt area prevents the onset of these symptoms, and if this area is transplanted into a normal animal the symptoms will
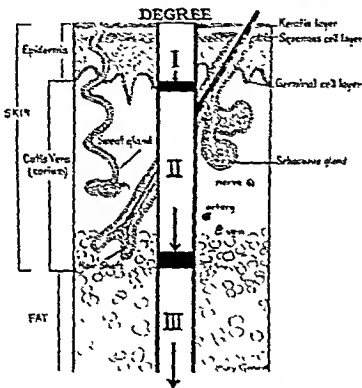
Fig. 14.—Diagrammatic representation of classification of burns. (Erb, Morgan and Farmer: Annals of Surgery, 117, 234.)

appear in that animal. Such facts suggest that some at least of the symptoms are due to the absorption of toxins from the burnt surface, but there is no agreement as to the nature of the toxin. Histamine may be liberated and may be responsible for the shock. A deep but limited burn may be shut off from the general circulation by local thrombosis, so that general toxic symptoms fail to develop.

Another factor which may be of even greater importance is concentration of the blood, which rapidly occurs in superficial burns owing to a great outpouring of fluid through the damaged capillaries into the subcutaneous tissue. This sudden local edema may lead to a remarkable concentration of the blood as shown by hemoglobin estimation (Underhill), and this leads in turn to circulatory failure and oxygen starvation

CHAPTER III

GANGRENE

Gangrene is death or necrosis of a part en masse. If the tissues are dry and become dessicated no bacterial decomposition will occur, whereas if they are wet it will.

The death of a part may naturally be brought about in a great variety of ways, so that it is difficult to give a clear and simple classification of the causes and clinical varieties of gangrene. Speaking very generally, however, it may be said that gangrene is due either (1) to interference with the circulation of the part, or (2) to the action on the tissues of bacterial toxins. In ordinary clinical practice by far the more important is the first of these groups. Frequently the two are combined.

A very useful clinical classification is into *dry* and *moist gangrene*. Dry gangrene is caused by a sudden arrest of the arterial blood supply to a part, especially to a portion of a limb. The blood drains out of the tissues, which become dry and shrivelled. Moist gangrene is due to the second great cause of gangrene, namely, the action of bacterial poisons on the tissues.

DRY GANGRENE

The most characteristic example of dry gangrene is that known as senile gangrene, in which the gangrene is a slow and gradual process the result of occlusion of the artery to the part by atheroma with a super-added thrombosis. It is most commonly seen in the foot, and usually begins in the big toe. In other cases the obstruction is more sudden, owing to the impaction of an embolus or the ligation of one of the main arteries to the part. In health the collateral circulation is usually quite adequate to supply the call for additional blood, so that gangrene does not develop. If, however, there is widespread vascular disease, if the heart is weak, if the resistance of the tissues is lowered by the long illness of the patient, the call for help, although indeed heard, can not be responded to, and the part will die. In deciding, therefore, upon the ligation of a main artery these considerations must be borne in mind.

The tissues being drained of their blood, the part becomes dried up and mummified. The skin is wrinkled, and at first is greasy and more or less transparent owing to the liberation of fat from the tissues, but soon the hemolysis of the red blood corpuscles leads to a discoloration at first greenish and finally black from the sulphide of iron which is formed. The term mummification is a singularly appropriate one, for the dry and shrivelled foot is exactly like that of a mummy, and when removed may be preserved dry and intact for an indefinite period. The dryness, however, is most marked at the surface where evaporation is free, and in many cases the interior may retain a considerable amount of moisture. Neuralgic pains are frequent and troublesome; they may be due to an accompanying neuritis.

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The tissue cells undergo the ordinary changes characteristic of *necrosis*. The cytoplasm loses its normal granular appearance, and becomes hyaline or vacuolated. The muscle fibres lose their transverse striations. The nuclei become broken up into fragments (karyorrhexis), or dissolve and lose their staining properties (chromatolysis). The red blood cells are hemolyzed, with liberation of the hemoglobin.

A very definite bright red *line of separation* soon appears between the living and the dead tissue. This line indicates a process of inflammation due to the contact of the dead with the still living tissue. There is a dilatation of vessels and an exudation of leucocytes, and into the inflammatory exudate granulations begin to sprout from the living tissue. These granulations soon erode the dead tissue at the line of junction, and

Fig. 16.—Dry gangrene (Coley).

in course of time complete separation may occur. As the blood supply of the skin and subcutaneous tissues is less abundant than that of the muscles and bone, the destruction of the former will proceed further up the limb than that of the latter, so that the resulting stump will be conical in form.

Dry gangrene may be due (1) to gradual vascular obstruction as is seen in senile gangrene, and the allied conditions of diabetic gangrene, thrombo-angiitis obliterans, and Raynaud's disease; (2) to more sudden vascular occlusion as in embolism, thrombosis, ligation, or injury of the vessels; (3) to extreme cold; or (4) to the action of escharotics.

Senile Gangrene.—The arteries, particularly those of the leg, are frequently so occluded in old people as the result of atheroma or of medial sclerosis complicated by atheroma (see Chapter XXV) that a mere

trickle of blood reaches the part. No pulse can be felt at the ankle in the rigid and tortuous vessels, and the foot is cold and numb. The calcified vessels form a striking feature in an X-ray picture. The tissues are just alive and nothing more, so that an injury of a trifling nature, such, for instance, as may be received while cutting a toe-nail, may give rise to a slight inflammation which is yet sufficient to produce extensive stasis in the sluggish blood stream, and results in the development of gangrene. Thrombosis of the narrowed vessel may complete the occlusion, in which case the gangrene will develop spontaneously.

The gangrene usually commences in the big toe as a dark-blue patch, or an indolent sore may appear, which in such circumstances should always be regarded with grave suspicion. The condition advances slowly but steadily, for the presence of the dead tissue gives rise to inflammation, which in turn is followed by stasis and gangrene, until a level is reached at which the inflammatory reaction is sufficiently active to lead to ulceration (Fig. 16). The rate at which the line of demarcation forms affords a hint as to the prognosis. Rapid formation indicates a more satisfactory condition of the circulation than a slow and long drawn out process.

It not infrequently happens that after the line of demarcation has formed the upward spread of the gangrene recommences, owing to the low vitality of the tissue being unable to cope with the inflammation at the junction between the dead and living tissue. It is obvious that under such circumstances operative interference is not to be lightly undertaken, for flap after flap may become the seat of gangrene at ever higher levels.

Diabetic Gangrene.—Diabetic gangrene may be regarded as a form of senile gangrene in which the process is modified by the presence of sugar in the tissues which offers an ideal pabulum for bacterial growth. It is confined to elderly persons, and is essentially due to arteriosclerotic changes in the vessels either occurring coincidentally or arising as the result of injurious substances in the blood.

Its onset is exactly like that of senile gangrene, so that in every case of apparent senile gangrene the urine should be tested for sugar. It begins as the result of a slight injury, and usually appears on the big toe or on the sole of the foot where a perforating ulcer may be formed. At first the process is a dry one, but the parts soon become moist, swollen, edematous, and of a dusky red color, owing to the entrance of bacteria. The upward extension is much more rapid than in senile gangrene, and there is little tendency to self-limitation by the formation of a line of demarcation.

It must be remembered that in senile gangrene sugar may make a temporary appearance in the urine, only to disappear when the gangrenous part is removed.

Gangrene Due to Thrombo-Angiitis Obliterans.—A form of gangrene which is closely allied to senile gangrene may occur in young men, usually Russian Jews, between the ages of 20 and 40. The vascular lesion, a combination of endarteritis obliterans and thrombosis, but affecting the veins as well as the arteries, is fully described in Chapter XXV. The vessels of the feet are the chief suffers. The patient suddenly feels pain, burning, and tingling in the feet, which become pale and cold, and no pulse can be felt at the ankle. Gangrene of the toes may develop, which pursues the same course as senile gangrene.

Gangrene Due to Raynaud's Disease.—In Raynaud's disease a condition of "symmetrical gangrene" may develop, affecting the fingers more often than the toes. It is due to spasm of the arterioles, the basis of which is supposed to be a neurosis. Attacks of local syncope, in which the part becomes pale and cold, are followed by attacks of local asphyxia, in which the great dilatation of the vessels leads to an extremely sluggish circulation, so much so indeed that stasis and finally dry gangrene may develop.

Gangrene Due to Sudden Vascular Occlusion.—The occulsion may be due to embolism, to thrombosis, or to the ligation of a large artery.

Embolism.—When the vascular system is in a state of health the sudden occlusion of a vessel by an embolus is unattended by any untoward consequences, except in the case of the end arteries to certain of the viscera, when infarction may result. Even when the main artery of a limb is tied, the collateral circulation is sufficient to maintain the nutrition of the parts. When, on the other hand, the vessels are the seat of widespread arteriosclerosis, such a sudden occlusion is frequently followed by gangrene.

The first evidence of obstruction is intense pain at the point of impaction of the embolus. Pulsation in the vessel is normal above the obstruction but absent below it. The part affected becomes quite white at first, although the collateral circulation may restore the color to some portions of it. Dry gangrene soon develops, dry, because the venous outflow is unimpeded. If, however, the embolus is a septic one, as is usually the case when it originates in an acutely inflamed heart valve, or if bacteria gain entrance from without, the gangrene will develop into the moist variety.

Arterial thrombosis is usually due to disease of the wall of the artery, the narrowing of the lumen and the roughening of the surface being the important factors. Occasionally, however, it may be due solely to certain infective and exhausting diseases, of which the principal is typhoid fever.

Trauma may so injure the vessels of a limb that gangrene results at some distance from the site of injury, a condition known as indirect traumatic gangrene. The vessels may be ruptured by a direct injury, such as the passage over the limb of a cart wheel, or they may be torn by a fragment of broken bone. If the artery alone is damaged the gangrene will be dry; if the vein also is injured the gangrene will be moist.

Gangrene Due to Cold.—Intense cold produces frost-bite in two ways: (1) by causing such extreme contraction of the small arteries that the tissues die as the result of the anemia; (2) by the direct action of the cold on the tissues, a factor of minor importance. The vascular changes, however, may not only be disastrous because of the extreme constriction, but also because of the extreme dilatation which follows unduly rapid thawing-out of the part. If the frozen part be exposed to undue heat the vessels dilate to such an extent that stasis and thrombosis occur, so that a limb which could have been saved owing to death of the tissues not having actually occurred may be sacrificed as the result of injudicious treatment. The gangrene is of the dry variety, and follows the same course as in the senile cases.

Gangrene Due to Escharotics.—A strong acid or a strong alkali applied

locally will produce necrosis. The former gives rise to dry gangrene, for the acid coagulates the fluids of the part; the latter gives rise to moist gangrene, for the alkali causes liquefaction of the tissues.

Carbolic acid, even in so weak a dilution as 1 in 100, may produce gangrene of a finger when applied in the form of a soak. A 1 per cent solution will produce gangrene in 24 hours, a 2 per cent in 12 hours, and stronger solutions in even shorter time. The gangrene is due in part to thrombosis of the vessels, in part to direct action of the poison on the tissue.

Bacterial Synergistic Gangrene.—The condition known as postoperative progressive bacterial synergistic gangrene has already been described on page 28.

MOIST GANGRENE

The essential difference between moist and dry gangrene is that in the former the venous blood is retained in the part, as a result of which saprophytic bacteria are enabled to flourish abundantly upon the dead tissue, and produce extremely marked putrefactive changes.

The disease is seen in characteristic form as the result of injury to the main artery and vein of a limb; no fresh blood can enter, so that the tissues die, and no blood can leave the part, so that liquefaction and bacterial infection occur. The limb is cold, pulseless, swollen, and edematous. The color varies between dark-red, green, purple, and black, owing to the sulphuretted hydrogen produced by the putrefactive bacteria acting upon the liberated hemoglobin with the production of sulphide of iron. The skin, which is moist and macerated, becomes raised into blebs which contain foul-smelling fluid or gas. The horrible odor is due partly to nitrogenous products such as indol and skatol, partly to non-nitrogenous products such as sulphuretted hydrogen, butyric acid, and lactic acid.

The disease spreads rapidly up the limb, and there is little attempt at any formation of a line of demarcation. Indeed before such a line can be formed the patient is usually dead as the result of septic absorption. The constitutional symptoms are always grave, in marked distinction to the condition of the patient in dry gangrene.

In addition to gangrene resulting from injury to the main vessels of a limb the following are the principal varieties of moist gangrene: gangrene from acute inflammation, bed-sores, gas gangrene, phagedena, and cancrum oris.

Gangrene from Acute Inflammation.—When an inflammatory exudate is rapidly formed in a dense and unyielding tissue, gangrene may ensue owing to the pressure of the exudate upon the vessels and the consequent cutting off of the blood supply. As the result of injury the deeper tissues may be badly torn whilst the skin escapes comparatively easily. Should infection supervene the pressure of the exudate on the vessels may cause extensive gangrene.

The best examples of inflammatory gangrene, however, are provided by boils, carbuncles, and necrosis of bone. The effect is particularly noticeable in bone, where the vessels are confined within such rigid canals that a mild degree of inflammatory swelling may result in the death of a portion of bone, especially if the periosteum be stripped off the bone by the formation of pus. The core of a boil and the slough of a carbuncle
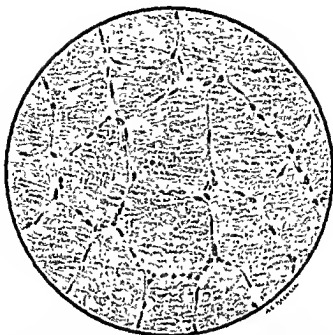
Fig. 17.—Gas gangrene. Normal muscle in transverse section, just beyond the edge of the spreading gangrene (British Medical Research Committee).
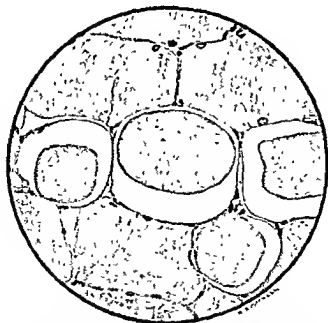
Fig. 18.—Gas gangrene. Muscle from as nearly as possible the visible advancing edge. Note the marked contrast between the dead coagulated fibers, which are separated off from their sheaths, and the paler normal fibers (British Medical Research C-----....
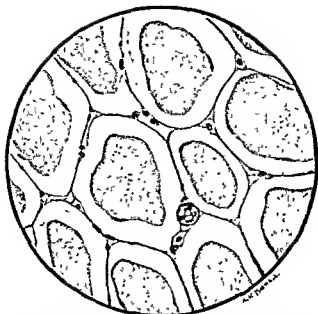
Fig. 19.—Gas gangrene. All the fibers are here degenerated, but their sarcolemmal nuclei still appear intact. Separation of the fibers from their sheaths is everywhere complete (British Medical Research Committee).
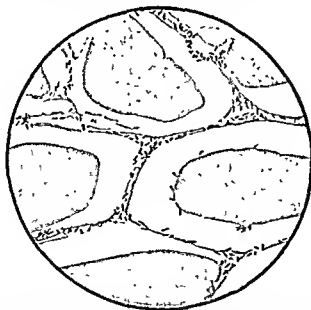
Fig. 20.—Gas gangrene. This shows the distribution of organisms at a comparatively early stage. There are large numbers of bacilli in the reticulum, but they have not yet invaded the fibers. This stage is slightly more advanced than that depicted in Fig. 19 and the nuclei of the sarcolemma have disappeared (British Medical Research Committee).

are examples of gangrene due to the same cause, and are to be distinguished from the molecular necrosis seen in an abscess of looser tissues.

Bed-sores.—A bed-sore is an example of pressure gangrene, developing over the sacrum, buttocks, and heels. Pressure alone, however, will not produce a bed-sore, for a healthy person may lie in bed for a year without developing one. The additional factors are a devitalized condition of the tissues as the result of old age or long illness, hypostasis from feeble circulation, and occasionally disease or injury of the spinal cord, which gives rise to an acute bed-sore. The only difference between an acute and a chronic bed-sore is the remarkable rapidity with which the former develops and spreads, and the fact that occasionally it does not develop at one of the usual points of pressure. It is not due, as used to be thought, to disturbance of hypothetical trophic centres in the spinal cord, but is more probably due to capillary stasis from injury to the vasomotor nerves.

The essential cause of a bed-sore is thrombosis due to continued pressure. A dusky reddish patch appears at the point of pressure, and the color deepens till it may be almost black. Blisters may rise and burst, and a greyish black slough forms which gradually separates, leaving a large granulating surface. The sore may be of any depth, and not infrequently exposes the underlying bone. Bacterial infection is invariable, and the resulting septic absorption is a most serious feature of the condition.

Gas Gangrene.—Gas gangrene, a condition formerly known as acute traumatic emphysematous gangrene, although fortunately comparatively rare in civil practice, was so appallingly prevalent during the first world war that great advances have been made in our knowledge of the disease.

The *bacteria* causing the condition are three in number, all of them anaerobic bacilli: (1) Bacillus welchii or B. aerogenes capsulatus; (2) Vibrion septique, probably identical with the bacillus of malignant edema; and (3) Bacillus oedematiens. To these may be added a fourth, Bacillus sporogenes, which, although neither causal nor gas-producing, is responsible for much of the horrible odor so characteristic of the disease.

These bacteria are putrefactive. They have the power of breaking down dead tissue, and their toxins and the gases they produce may seriously impair the vitality of living tissue, but they are unable of themselves to gain a footing in healthy tissues. In the war wounds the preliminary injury was due either to the direct trauma produced by a projectile, or to the cutting off of the blood supply to the part. The anaerobic bacteria introduced into the wound on pieces of clothing, etc., then got, and seized, their opportunity.

The disease is essentially an affection of muscles, and the connective tissue may be, at first at any rate, comparatively little affected. Moreover the spread is longitudinal rather than transverse. The infection readily spreads from end to end of a muscle, but may be unable to spread from one muscle to another.

The affected muscle is at first dull and opaque, brick red in color, and resembles cooked meat. Even at this stage it is dead, for it does not contract when pinched nor bleed when incised. Bubbles of gas which can be pressed up and down between the fibers may be evident to the naked eye. Soon it softens and becomes diffluent, the color changing to green, brown, or black. The exudate is blood-stained. Gas can be felt in

3

CHAPTER IV

THE INFECTIVE GRANULOMATA

TUBERCULOSIS

Tuberculosis is the most important killing disease affecting mankind. It is responsible for no less than one-seventh of the deaths in the world. The disease may attack any tissue, but in addition to the lungs may be mentioned the lymphatic glands, the bones and joints, the spinal column, the brain, the eye, the intestine, the peritoneum, the Fallopian tube, the kidney, bladder and testicle, and the skin.

The Tubercle Bacillus.—Tuberculosis is caused by Bacillus tuberculosis, the discovery of which by Koch in 1882 served at once to establish the identity of a number of conditions such as lupus, Pott's disease, scrofula, and phthisis, which were previously regarded as quite distinct entities. The bacillus is a thin curved rod, from 3 to 4 μ in length, sometimes presenting a beaded appearance, staining with difficulty, and best shown owing to its acid-fast properties by the Ziehl-Neelsen method. It does not grow on ordinary media, but on glycerine egg an abundant wrinkled growth makes its appearance after the lapse of two or three weeks.

There are two varieties of tubercle bacilli of importance in human pathology, the human and the bovine. The two varieties cannot be differentiated with certainty on morphological grounds. They can readily be distinguished in culture and by animal inoculation. On glycerine agar the human type grows readily, the bovine not at all; the former is said to be eugonic, the latter dysgonic. Intravenous injection of a minimal dose of human tubercle bacilli in a rabbit will not result in death, whilst with the bovine type the animal will die of general miliary tuberculosis.

The disease in man may be caused by either type. Pulmonary tuberculosis in the adult is nearly always due to the human type. In children the bovine type is often the infecting organism, particularly in disease of bones and joints and of glands. The incidence appears to vary markedly in different localities, depending on the nature of the milk supply. In Edinburgh John Fraser found the bovine bacillus in 58 per cent of his cases of bone and joint tuberculosis in children, and in the same city Mitchell found that 90 per cent of the lymphatic gland tuberculosis in children was bovine in origin. That, however, was in 1914. Much lower figures are reported by workers in England and America. In 392 cases of bone and joint tuberculosis investigated by the British Royal Commission there were only 20 per cent of bovine infections, and the Imperial German Board of Health found only 5 bovine infections in 99 cases of all ages. The human type of bacillus is that responsible for most cases of bone and joint tuberculosis in the adult.

Infection.—All tuberculosis is due to infection with the tubercle bacillus,

but the problem of infection cannot be stated thus baldly. It is not the bacillus alone which has to be considered. In every case there are two elements concerned, one destructive, but the other conservative. There is the seed, but there is also the soil. The seed, as Osler put it long ago, may fall by the wayside, or on stony ground, or among thorns, or finally it may fall on good ground and bring forth fruit an hundredfold. The seed of tuberculosis is so universal that it falls on practically all mankind, but fortunately a high natural or it may be an acquired racial immunity is so general that in most cases the soil remains barren, but for a healed tubercle here and there indicating the powers of defense. As we shall see, however, the term healed tubercle is not really justified. Although the active process may to all appearances have died out, and the lesion seems to consist of nothing but a mass of fibrous tissue, yet inoculation experiments will almost invariably reveal the presence of living tubercle bacilli.

Moreover, a fundamental distinction must be drawn between primary and secondary infection. From the evidence furnished by the autopsy room and by tuberculin tests we know that a large proportion of the population is infected by the tubercle bacillus before the age of puberty. But this does not imply that they are suffering from tuberculous disease. Tuberculosis as it occurs in adults is due to reinfection. The more or less chronic course pursued by the disease in adults is an indication that the patient has already been partially immunized in childhood. In peoples, such as those of remote and uncivilized countries, who have not had the benefit of this protective inoculation, tuberculosis spreads both amongst the population and throughout the body of the patient with the fury of one of the zymotic diseases.

The natural resistance of the body comes to assume great importance in cases in which the tuberculous disease is secondary to a focus which keeps up a constant supply of infection. In tuberculosis of the bladder the condition is kept active by the passage of bacilli down the ureter from a tuberculous kidney, and tuberculous peritonitis in the female is frequently secondary to infection of the Fallopian tubes. In these cases if the primary source of infection in the kidney or tubes be removed, the secondary lesion will often look after itself.

Owing to a lowered resistance, however, the soil may become suitable. Such a low resistance may be congenital, transmitted, and familial; or it may be acquired from unsuitable environment, lack of nourishment, or the depressing effects of some other disease such as measles or influenza. A recognition of the importance of the soil is of great moment in matters of treatment, for though it be not possible to attack the bacillus by direct means, we may yet make the soil so unsuitable that a natural cure is effected.

Mode of Entrance —The two chief methods of infection in man are inhalation and ingestion. The former is responsible for pulmonary tuberculosis, the latter for tuberculosis of the alimentary tract and the lymph nodes which drain it. Infection through the skin may occur in those engaged in "dangerous occupations," i. e., pathologists (in whom a skin lesion known as post-mortem wart or verruca necrogenica may develop), butchers, hospital orderlies (cleaning sputum cups, etc.), and nurses. The regional lymph nodes are often infected, but general infection is

uncommon. Congenital infection, the bacilli passing through the placenta, is a possibility, but must be very rare.

Alimentary infection is by tuberculous milk, so that the bacillus is commonly of the bovine type. The tonsils are the first structures to be exposed to infection, and at least 5 per cent of the tonsils removed show microscopic evidence of tuberculous infection. In the intestine the bacilli are taken up by mononuclear phagocytes and carried through the lymphoid tissue of the mucosa into the submucous coat.

Infection by inhalation may be due to bacilli being inhaled in dust (dried sputum) or in the tiny droplets of moisture coughed out by patients with pulmonary tuberculosis. The bacilli may also be inhaled into the lung if infected material is deposited in the mouth as in the case of children whose hands become infected and who introduce bacilli into the mouth by sucking the fingers. As pulmonary tuberculosis is much the most common form of the disease, so inhalation is the usual method of infection.

The Miliary Tubercle.—However varied may be the pathological manifestations of the tuberculous process, the initial lesion is almost always the miliary tubercle, although occasionally we meet with a more diffuse reaction, the tuberculous granulation tissue. The early stages in the development of the tubercle are best observed in the experimental animal, but it must be borne in mind that the response of the tissues to tuberculous infection may be very different in the tubercle-free animal from that which occurs in an already tuberculous animal, the latter, of course, being the type of lesion observed in human pathology.

Two types of reaction are met with in tuberculous lesions. The first is a pure cellular proliferation; the second is represented by an outpouring of leucocytes and serum, and is exudative or inflammatory in character. The pure and characteristic reaction to tuberculous infection for the first time, provided that the infection is not too heavy, is a proliferation of the cells of the part—not the parenchymatous cells, but cells which are probably reticulo-endothelial (histiocytic) in origin. The cells are larger than a leucocyte, and possess a large vesicular nucleus and a clear cell body with processes which may anastomose with those of its neighbors, thus giving rise to an apparent reticulum. It is to these cells that the name epithelioid is applied. The reticulum is known as the *epithelioid reticulum*. A small mass of pale-staining tissue is thus formed which becomes visible to the naked eye as a tiny grey translucent nodule at about the end of the second week, and is then known as a *miliary tubercle* from its approximation in size to that of a millet seed (Fig. 21).

In addition to the epithelioid cells one or more cells many times the size of their fellows may be seen situated usually toward the center but occasionally at the periphery of the tubercle. These cells contain many nuclei, often twenty or more, which are characteristically grouped at one or other pole or arranged around the periphery, although a few may be found in the center. These cells are true foreign body giant cells, and usually contain tubercle bacilli. They are apparently formed by the fusion of a number of epithelioid cells, and it is probable that both types of cell represent a reaction against the fatty and waxy envelope of the bacilli, which cause them to be treated as foreign bodies. Whilst giant

cells are very characteristic of tuberculosis, they are found in other chronic inflammations such as syphilis and actinomycosis; they are also seen clustered around foreign bodies in the tissues such as a piece of a silk suture, tiny particles of bone, etc. Moreover they may be absent from tuberculous tissue. Tuberculosis sometimes takes a slow and chronic form in which the lesions are made up of epithelioid cells with no giant cells nor other half mark of the disease. These cases present a certain difficulty in diagnosis unless one is aware of their existence.

For the first few days the tubercle consists entirely of the phagocytic epithelioid cells and giant cells, although in cases where a very large dose has been used the irritation may be so great as to cause the temporary outpouring of a flood of polymorphonuclear leucocytes. By the end of

Fig. 21.—Tubercle showing epithelioid cells, peripheral lymphocytes, giant cells, and commencing caseation in center. × 100.

a week *lymphocytes* begin to make an appearance, small dark cells with a darkly staining nucleus and scanty cytoplasm, identical in structure with the lymphocytes of the blood, but probably derived from the cells of the perivascular lymphatic sheath or other lymphoid tissue. At this stage the tubercle presents, in hematoxylin and eosin preparations, a dark blue peripheral ring of lymphocytes surrounding a central pink mass composed of endothelial cells with their pale nuclei, and an occasional giant cell, intermingled with which are a few blue lymphocytes.

The tubercle is non-vascular. The reaction is a cellular proliferation, and does not include the formation of any new blood vessels. This non-vascularity has an important influence on the production of caseation.

By the end of the second week *caseation* has begun to appear in the center of the tubercle follicle. The cells in the center lose their outline

and structure, undergo necrosis, and appear to fuse together, so that a granular structureless material is formed, staining diffusely with eosin, dry and cheesy in consistence. This coagulation necrosis is due partly to lack of blood supply, partly to the action of the bacterial toxins. The tubercle bacillus produces no exotoxin, but on disintegrating it liberates a slowly acting endotoxin which causes necrosis of the surrounding tissue. This disintegration is effected by the action of the cells which make up the tubercle follicle.

Reference has already been made to the fact that the type of reaction to an injection of tubercle bacilli depends largely upon whether the animal is tubercle-free or already suffers from tuberculosis. In the former case it is essentially sluggish and is proliferative rather than inflammatory. In the latter the response is rapid and is essentially inflammatory and exudative; there is an outpouring of leucocytes and of serum. The reason is that the animal is in a state of allergy, and the chief manifestation of the allergic state is this immediate inflammatory response. The difference in the two reactions is beautifully shown by skin inoculation tests, and this forms the basis of the well-known von Pirquet cutaneous reaction.

In the course of two or three days the inflammation subsides and is succeeded by the slow cellular proliferation which results in the formation of a tubercle. It will be obvious that this must be the course of events in the spread of human tuberculosis throughout the body, for once the initial lesion has become established the patient is in a constant condition of allergy.

The subsequent course of the disease depends on the balance between the forces of destruction and conservation. The sequence of events may be one of the following:—

1. New tubercles may be formed in the adjoining tissue, which coalesce with the original tubercle till large areas of caseation are produced. These areas are usually very irregular in outline, but in the brain and more rarely in the liver large spherical "solitary tubercles" may be formed.

2. The irritation produced may be so great, owing to the presence of excessive numbers of bacilli, that a typical acute inflammatory reaction is the result, with abundant migration of leucocytes and exudation of serum, obscuring to a large extent the tuberculous nature of the infection. Such a course of events is well seen in tuberculous meningitis and acute pneumonic phthisis.

3. In some cases there is an intermediate condition with the production of a granulation tissue without caseation, identical with that of ordinary inflammation save for the presence of numerous tubercles. This may be seen in the synovial membrane of joints, in the hyperplastic form of tuberculosis which occurs at the ileo-cecal junction, and in other positions.

4. Finally, the reaction on the part of the tissues may be sufficient to limit the spread. The fibroblasts proliferate, forming a fibrous zone around the tuberculous area walling it in, so that the caseous area becomes enclosed in a fibrous capsule. In such an area bacilli may remain viable for long periods, but in a quiescent condition, so that the patient shows no symptoms of the disease. Or the fibrous tissue may invade the

follicle, converting it into a fibrous mass, in which lime salts may be deposited in considerable amount, the result being a so-called *healed tubercle*. This last change is fortunately of common occurrence, as the calcareous masses so frequently found in the lungs and mediastinal glands testify. Even in the healed tubercle, however, living tubercle bacilli can usually be demonstrated by animal inoculation.

Spread of the infection may occur in four ways: (1) permeation, (2) along natural passages, (3) lymph spread, (4) by the blood stream.

Permeation is the chief means of local extension. Phagocytes containing the bacteria transport them into the neighborhood of the original focus, making their way along the tissue spaces. In many organs this gives rise to a lesion of irregular shape, but in such a structure as the brain where there are facilities for spread in every direction there may be formed a tuberculous tumor-like mass, the "solitary tubercle" or tuberculoma. Spread along the *natural passages* is best seen in the case of the bronchi and ureter. The *lymphatics* are the most important route of spread. The regional lymph nodes are therefore commonly involved, and if the bacilli are not arrested by the nodes and reach the thoracic duct, they will pour into the blood. The *blood stream* therefore may be infected by way of the lymphatics, or occasionally by the tuberculous process involving the wall of a blood vessel. When bacilli are scattered broadcast throughout the body by the blood, the result is *general miliary tuberculosis*, a condition in which the rapid growth and breaking down of the bacilli results in a severe toxemia accompanied by fever, and usually terminating in death in the course of a few weeks. Tiny tubercles are found in almost every organ in the body, and the end is often due to tuberculous meningitis.

Tuberculous Pus.—Typical caseous material is dry, granular, and cheese-like. It is high in unsaturated fatty acids which inhibit the action of proteolytic ferments. When these acids become saturated, either through the administration of iodides or as the result of a natural process, the ferments have free play, and may produce rapid softening and liquefaction of the caseous material. The result is the formation of o thick creamy fluid, to which the name of tuberculous pus is given, ond the condition is called a *cold abscess*. The fluid is not true pus, but consists mainly of fatty debris floating in a serous fluid, intermingled with which are a few necrotic cells. It is usually sterile.

A *cold abscess* is so named because it is a soft, fluid swelling without the signs of acute inflammation. It is slow and insidious in onset and may be mistaken for a cyst, a gumma or a fatty tumor. The wall of the abscess is lined by granular, caseous material, which may contain tubercle bacilli. The outer layers consist of granulation tissue in which caseation has not yet occurred.

Opening and drainage of a tuberculous abscess, even under the most aseptic of conditions, is almost certain to be followed by invasion by pyogenic organisms. The condition is then said to be one of *mixed infection*, and the last state of that man is much worse than the first, for such constitutional symptoms as hectic temperature, wasting, and night sweats appear and dominate the picture. For this reason drainage of a tuberculous abscess is almost invariably bad practice.

SYPHILIS

Syphilis is an infectious disease caused by Spirochaeta pallida (Treponema pallidum) which enters through the skin or mucous membrane, producing a local lesion, and is then disseminated by the blood stream throughout the body. The disease occurs in two forms, the congenital and the acquired.

The general appearance of the Spirochaeta pallida with its tenuous body and sharp spirals is known to everyone (Fig. 22). The epithet pallida is earned by the pale appearance of the organism in stained smears.

It is present in all syphilitic lesions, although much more readily demonstrated in primary and secondary lesions than in those of the tertiary period. Any lesion, therefore, of whatever date, from the surface of which there is a discharge, must be regarded as potentially infectious. During the earlier stages the organisms are found in the circulating blood. The most dangerous lesions are the primary sore and such superficial lesions of the skin and mucous membranes in the florid secondary stage as condylomata and mucous patches.

The best methods of demonstrating it are dark-field illumination and the Levaditi method of staining. The dark-field method is of extreme value in examining the discharge from a primary (or secondary) lesion, the active to-and-fro movements of the brightly illuminated spirochetes against the black background rendering their detection easy. The Levaditi method of silver impregnation is the only means by which the spirochetes can be demonstrated in the tissues. The spiro-

Fig. 22.—Spirochaeta pallida. × 1000.

chetes are stained black, but artefacts are common, so that the method is only of value in the hands of an expert—and even he may be in error.

The spirochete is a delicate organism which is readily killed outside the body by drying and by weak antiseptics. It is grown in culture only with great difficulty. It is strictly anaerobic, and is best cultivated on serum agar containing a small piece of sterile tissue.

The disease can be transmitted experimentally to animals, not only to the higher apes, but to the lower monkeys and even to rabbits. It is only when the virus is inoculated at certain sites that the disease will develop with certainty: the genital organs in the monkey, the scrotum and testicle in the rabbit. Elsewhere the spirochete fails to gain a hold. The work of Brown and Pearce on the rabbit is especially worthy of note.

For clinical purposes the disease is usually divided into three stages, primary, secondary, and tertiary, but the essential pathology in every stage is the same. Whether it be a primary chancre, a skin lesion, a mucous patch, an aortitis, a gumma, or a brain lesion in general paresis, the nature of the process is uniform, varied only by accidents of time and opportunity.

The several stages are separated by curious intervals of latency, during which the patient may experience no symptoms. During these periods, however, the spirochetes are by no means latent. It is the distinction, which we have already observed in tuberculosis, between infection and disease. The latent period does not indicate that the organisms are spreading to distant and hitherto uninfected organs, for they have already reached them by the blood stream. It signifies rather that the tissues are undergoing a vital change, are developing a hypersensitiveness, on account of which they will react to the irritant with the production of the symptoms of disease. The organs differ in the time they take to develop this hypersensitiveness, the skin early, the central nervous system late, so that disease appears at different periods, but infection is there from a very early date. It is significant to note that Brown and Pearce in their experimental work on the rabbit have shown that although the defensive reaction may succeed in neutralizing the power of the spirochetes to produce disease, the infection is never abolished.

The same workers have formulated what they call the law of inverse proportions. The duration of a lesion, that is to say an active manifestation of the disease, is inversely proportional to the intensity and extent of the local reaction. The same is true for the disease as a whole, so that severe early lesions are likely to be associated with mild manifestations in the later stages, whereas disastrous late results may have been preceded by early lesions so slight as to have escaped the notice of the patient, a fact which considerably increases the difficulties of diagnosis.

The different stages recognized by the clinician represent varying stages of reaction rather than varying stages of infection. Indeed the spirochetes are disseminated throughout the body and a condition of syphilitic septicemia set up at an extraordinarily early date. In patients who have died from accident when the primary sore was still fresh, the infection was found to have spread through the lymphatic vessels and the lymph nodes and to have reached the thoracic duct, so that blood infection had almost certainly occurred in this the first stage of the disease. Neisser was able to demonstrate spirochetes in the central nervous system of apes 10 days after inoculation, even before a local sore had fully developed. As Clifford Allbutt remarks: "From the first the seed spreads secretly; and when the circulatory system is clotted up by the parasite the time for effectual intervention is past. 'Take these foxes while they are little.'"

Infection in the great majority of cases is acquired during sexual intercourse. It may occur, however, in sites other than the genital organs. Of these the most important are the lips, the fingers, and the nipple. The spirochetes usually enter through some crack or abrasion, but they may penetrate an uninjured mucous membrane.

Following the infection there is a latent period, usually of 3 or 4 weeks, but this may be as short as 2 or as long as 6. Long before this period has elapsed the blood stream is invaded, and systemic infection occurs, a syphilitic septicemia. At the end of the first latent period the primary lesion makes its appearance.

A second latent period now supervenes during which, although the spirochetes have been disseminated throughout the body, there is on

sign of their presence. At the end of from 2 to 3 months after infection the tissues of ectodermal origin have apparently acquired the power to react, and lesions appear in the skin, mucous membranes, and central nervous system. These lesions may persist for 6 to 12 months or more, leaving no trace except perhaps for some pigmentation of the skin.

Again the patient may have an intermission during which he thinks that all is well, but tissue changes in the internal organs are going on, slowly but remorselessly, and one, two, or it may be many years later, these begin to tell their tale.

Immunity.—Syphilis conveys a marked degree of immunity, so that reinfection is uncommon. But the immunity can be overcome, especially in the earlier stages of the disease. Its intensity depends on the local reaction; if this is defective the immunity will be weak. An animal may be immune to infection and yet may harbor the spirochetes in its tissues. If a rat is inoculated with Spirochaeta pallida it develops no chancre, no lesions or symptoms, yet the organs are found to be intensely infective a year later when inoculated into a rabbit. It appears probable that there are different races of spirochetes, so that immunity may develop for one race, but another race may produce reinfection.

Pathological Histology.—The clinical manifestations of syphilis are protean and complex, but the pathological histology is constant and simple. The syphilitic lesion consists of a mass of granulation tissue; it is a granuloma. In the primary and secondary lesions this tissue is vascular and highly cellular, and the condition may terminate in resolution. In the later or so-called tertiary lesions the new cells become converted into fibrous tissue, the vessels obliterated, with

Fig. 23.—Plasma cells. × 1300.

a resulting degeneration of the parenchymatous cells, so that there is either a diffuse scarring with atrophy of the parenchyma, or the formation of caseous masses called gummata. The early lesions occur in vascular, the later in relatively non-vascular organs.

The principal cells of the infiltration are lymphocytes and plasma cells. The latter are particularly suggestive of syphilis, although they sometimes occur in large numbers in other chronic inflammations (Fig. 23). Giant cells are found in the lesions of the later stages of the disease. It is evident that the pathology of syphilis may closely simulate that of tuberculosis, and it may be difficult to distinguish the lesions from those of other infective granulomas and from chronic inflammation. The microscopic picture is often highly suggestive, but rarely pathognomonic. The demonstration of spirochetes in the tissue is the most convincing evidence of the nature of the lesion, but this is not very easy and negative results mean nothing.

A brief summary of the varied lesions of syphilis may now be given, but the conditions of special surgical importance will be considered in greater detail in later sections.

The Primary Lesion.—The primary lesion or chancre commences as a nodule, not as a sore. In most cases, however, the surface becomes abraded, so that an ulcer is produced, the chief characteristic of which is the marked induration both of the floor and edges, which earns for it the
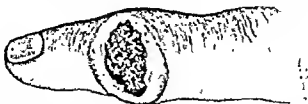
Fig. 24.—Chancre of the finger, four weeks old. (Edward Martin in Keen's Surgery.)

epithet "hard" (Fig. 24). It is of great importance to note that this induration does not appear for several days, else the correct diagnosis may be missed in the earliest stage. The induration is due to the cellular infiltration and formation of new tissue which is the essential pathological lesion in syphilis. It may be so marked as to give the chancre a feeling as
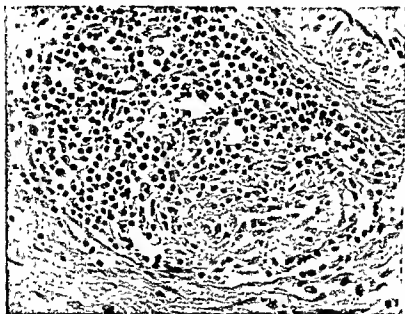
Fig. 25.—Perivascular reaction characteristic of syphilis. × 375. (Courtesy of Dr. G. H. Ewell, Jackson Clinic, Madison.)

of a button of cartilage when pinched between the finger and thumb. The floor of the ulcer is dull red, later becoming coppery and glazed, or it may be covered with a grey false membrane. The discharge is thin and watery, and contains the Spirochaeta pallida in large numbers. There is no pain, and the chancre is insensitive. The lesion heals in the course of a few weeks, and leaves no scar if there has been no destruction of tissues.

In congenital syphilis the primary lesion is in the placenta. There is therefore no primary stage in the child.

The *microscopic appearance* is that found in the early stage of all syphilitic lesions, but is lacking in distinctive features, and is much less readily recognized than the lesions of tuberculosis. Syphilis is mainly a disease of the blood vessels, and even at this early stage this characteristic is in evidence. There is a great formation of new vessels, and about these there is a perivascular accumulation of lymphocytes and plasma cells (Fig. 25). Large pale cells of irregular outline with vesicular nuclei may be seen. These are proliferating fibroblasts, which may later be responsible for the formation of scar tissue. The inner coat of the arteries may be thickened even thus early, a condition of endarteritis obliterans. There is stasis of the vessels from pressure of the accumulated cells, causing hemorrhage with the liberation of blood pigment which is responsible for the coppery pigmentation so characteristic of syphilitic lesions. The Spirochaeta pallida may be demonstrated by means of the Levaditi method.

Chancre and Chancroid.—The condition with which a chancre is most likely to be confused is chancroid or soft sore, an acute inflammatory lesion produced by Ducrey's bacillus, and acquired through sexual intercourse. The important points of distinction are as follows:

	Chancre	Chancroid
1. Incubation period.	2–4 weeks.	2–4 days.
2. Number	Single.	Usually multiple.
3. Type of lesion	Proliferative.	Destructive.
4. Induration	Marked.	None.
5. Discharge	Thin and serous.	Purulent.
6. Spirochaeta pallida	Present.	Absent.
7. Lymphatic glands	Not inflamed.	Inflamed, tender, suppurating.
8. Wassermann reaction . .	Positive after three weeks.	Negative.

It is of course possible to have a mixed infection, in which a chancre is superadded to a soft sore. In such cases the only certain method of diagnosis is the demonstration of the spirochete. It is therefore advisable to examine every case of soft sore for the Spirochaeta pallida, as the latter may be present in the sore for some weeks before the changes characteristic of a chancre make their appearance.

Primary Lymphatic Node Enlargement.—At the end of the first or second week after the appearance of the chancre the lymphatics leading from it may be felt as thickened cords, and the nodes in the groin on both sides become enlarged. They do not attain a size larger than a marble, are hard and shotty, discrete, and are not painful or tender. The condition ends in resolution, and the nodes return to their normal size.

The *Secondary Lesions.*—The secondary lesions are found mainly in the skin and mucous membranes, but the nervous system, the eye, and the bones and joints may all be affected.

At the end of the second latent period the patient commences to show

signs of *constitutional disturbance*. There may be a varying degree of *fever*. The blood shows an *anemia*, often marked, and there may be an increase in the lymphocytes. *Cachexia* is of frequent occurrence, the patient developing a pale, sallow complexion, and showing perhaps some slight wasting.

Lymphadenitis is one of the earliest and most constant features of this stage. The nodes throughout the body become enlarged and indurated, there is an absence of inflammatory changes, and the enlargement persists for several months and sometimes years. Enlargement of the epitrochlear and posterior cervical nodes is of special diagnostic value. Resolution ultimately occurs.

The *skin* is the seat of lesions bewildering in their number and variety and simulating many other skin diseases, but displaying certain common characteristics. They are symmetrical in distribution, polymorphous in type, so that several varieties may be present at the same time, thus differing from ordinary skin rashes, present an outline corresponding to a segment or the whole of a circle, possess a coppery tinge, heal as a rule without destruction of tissue, and respond readily to treatment. The particular lesion depends on the degree of the inflammatory process. The *macular* rash, resembling that of measles, results where the vascular changes are marked with but slight cellular infiltration. When there is an abundant collection of cells the lesion becomes *papular*. In the later stages it may become *pustular*, and rounded necrotic patches covered by a crust are formed, the condition termed *rupia*. Another late manifestation is a scaly eruption of the palms of the hands and the soles of the feet, a condition extremely suggestive of syphilis.

A common form of lesion of the skin is the *condyloma*. This is a flat elevation, moist, loaded with spirochetes, and extremely infectious. Condylomata occur where two skin surfaces are in contact and consequently moist, as in the anal folds, the vulva, and between the thighs.

The hair and nails are often affected, owing to the inflammation extending down into these appendages of the skin. The hairs fall out, giving rise to a partial alopecia, patches on the back of the head losing some but not all of the hair and having a "moth eaten" or "mangy" appearance. The nails become dry, brittle, and fissured, a condition of *onychia*.

Mucous Membranes.—In the mouth and pharynx *mucous patches* are of very common occurrence. They are flat raised patches, milky in color, surrounded by a narrow red border, and often likened to the track of a snail. Frequently they become ulcerated, and discharge great numbers of spirochetes. They also occur in the vaginal mucosa. They are due to inflammatory proliferation of the surface epithelium.

The Central Nervous System.—It used to be thought that involvement of the central nervous system occurred only late in the disease. It is now known that it may be one of the earliest organs involved. Examination of the cerebrospinal fluid shows the changes characteristic of meningeal irritation, namely lymphocytosis and an increase in the globulin content. The neuralgic pains and ocular palsies of the secondary stage are dependent on the same cause.

The Eye.—Iritis is of common occurrence at this stage and differs in

no way from that due to other causes. Retinitis may occur, but is more characteristic of the later stages.

Bones and Joints.—Periostitis is a common early sign, and may appear at the same time as the rash. Usually, however, it does not come on till a few months later. The bones commonly affected are the tibia, clavicle, sternum, and cranial bones. A painful, tender, elastic swelling forms over the bone. The pain is usually worse at night, owing to the increased vascularity when the patient is warm in bed.

One or more joints may show a subacute inflammatory swelling with little pain or tenderness. The knee is most often affected. The condition terminates by resolution.

The Tertiary Lesions.—Although no hard and fast line can be drawn between secondary and tertiary syphilis, the secondary lesions sometimes appearing late and the tertiary early, yet there are important differences between the two varieties. The tertiary lesions are not symmetrical, they affect the deep organs as well as the superficial structures, they contain few spirochetes, and they show a tendency to destruction which is not seen in the earlier lesions.

The lesions may be diffuse or more localized. The localized form is known as the gumma. It is much more easily recognized, so that it used to be thought that it was the commoner of the two. The reverse is the case, but it may be very difficult to be sure if a supposed diffuse tertiary lesion is really syphilitic or not.

As the result of the spirochetes settling in the tissues a slow inflammatory process is set up, and the part becomes infiltrated with small round cells and plasma cells, with an accompanying proliferation of fibroblasts. There is a formation of new vessels, and the result is a cellular granulation tissue, analogous to the granulation tissue that is sometimes formed in tuberculosis. The inner coat of the arteries of the part becomes much thickened, with narrowing of the lumen. In course of time the new connective-tissue cells become converted into fibrous tissue, the parenchyma cells atrophy, and extensive scarring follows (Fig. 26). Thickening of the base of the tongue and of the testicle are of value in autopsy diagnosis.

The lesion may be localized, in which case a *gumma* is formed. The proliferating cells give rise to a definite nodule, the center of which undergoes caseation, due mainly to deficient blood supply from obliteration of the vessels (Fig. 27). The caseation is seldom so complete as in tuberculosis, and traces of the original structure can usually be made out. Surrounding the caseous center are the usual lymphocytes and plasma cells, and further out there is a zone of proliferating fibroblasts or definite fibrous tissue. Giant cells similar to those of tuberculosis are of common occurrence, but are seldom so numerous as in the former disease. To the naked eye the gumma appears as a yellow homogeneous mass surrounded by fibrous tissue. When near the surface ulceration may occur.

The gumma when small may become invaded with connective tissue and fibrosed. As a rule, however, the caseous center remains unaltered. It does not liquefy, because the proteolytic ferment necessary for such liquefaction is neutralized by the large amount of unsaturated fatty acid present, which acts as an antiferment by virtue of its unsaturated state.
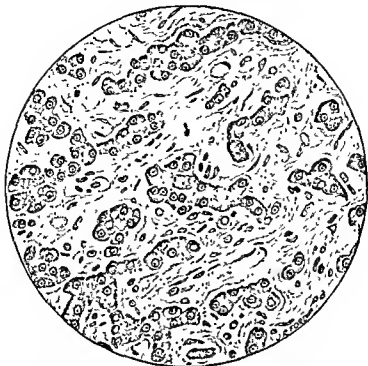
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Fig. 26.—Congenital syphilis of the liver. A good example of the diffuse infiltrative form of the disease.
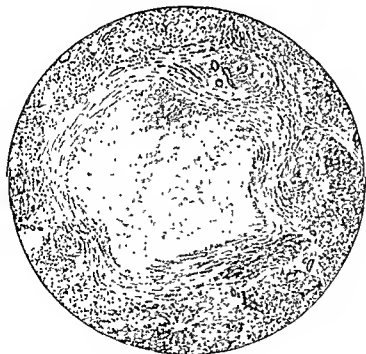
Fig. 27.—Gumma of the liver.

When saturation is produced by means of potassium iodide, the proteolytic ferment quickly asserts itself, and liquefaction and absorption are the result.

Although from the medical standpoint the diffuse inflammatory lesion is the more important, from the surgical the gumma claims first place, and it will therefore be considered here.

Any organ of the body may be affected, but the common sites are the skin, the mucous membranes, the viscera, the bones, and the nervous system.

The Skin.—A gumma may commence in the skin, in which case it usually ulcerates early. Or it may be formed in the subcutaneous tissue, appearing as a hard, painless mass, freely movable, which disappears readily under treatment. It may also involve the skin and ulcerate. The characters of the syphilitic ulcer have already been described (page 25). Its punched-out character, serpiginous outline, and wash-leather base are usually highly characteristic. It tends to heal at one point and break down at another, a method of spread responsible for the wavy character of the margin. When it heals it leaves a scar, at first pigmented, later becoming white. The knee is a favorite site for such scars.

Mucous Membranes.—The tongue may be the seat of a syphilitic glossitis. In the early stages the organ is swollen, red, moist and painful. The papillae disappear leaving the surface characteristically smooth, red and glazed. Oval-shaped ulcers may form, which must be distinguished from those due to malignant disease. The latter occur at the edge of the tongue, whereas the syphilitic ulcer may occur on any part, but particularly in the center. It is not uncommon for carcinoma to develop on a tongue already damaged by syphilitic glossitis. As sclerosis occurs the tongue becomes indurated, and the smooth surface is broken up by numerous cracks and fissures.

The *pharynx* may be the seat of gummatous ulceration. Perforation of the soft palate may occur. The subsequent fibrosis may cause marked deformity.

The *larynx* is liable to similar changes. There may be ulceration, and later scarring, which greatly interferes with the action of the vocal cords, giving rise to a characteristic hoarseness of the voice.

The Viscera.—Gummata may occur in any of the viscera, but the liver is the most frequently involved. The gumma may heal with fibrosis, giving rise to deep radiating scars in the organ, so that the surface may become lobulated. Large gummata of the liver are seldom seen nowadays. Syphilis of the testicle is perhaps of the most interest to the surgeon. The organ may become the seat of a gumma, which may remain for years as a hard resistant mass, or may break down and ulcerate through the scrotum. Much commoner is a diffuse infiltration with fibrous tissue, causing a uniform enlargement of the organ. In both cases there is a characteristic loss of testicular sensation on palpation. The condition has to be distinguished from tuberculosis and carcinoma.

The Bones.—Either gummata or a diffuse periostitis may occur. The gumma forms an ill-defined mass, which is both tender and painful. It is usually absorbed, but may break down and ulcerate. The tibia and the cranial bones are common sites. The condition may be mistaken for sarcoma.

The Nervous System.—To the physician the subject of cerebrospinal syphilis is of the first importance, but to the surgeon the chief lesion of interest is the gumma, which may produce all the symptoms of a cerebral neoplasm. It usually grows from the meninges, but may occur in the substance of the brain. It used to be a common lesion, but now has become a rarity. The Wassermann reaction is usually negative in the cerebrospinal fluid.

Congenital Syphilis.—Syphilis may be inherited from either the father or the mother. In all cases of paternal transmission the mother is also infected, although she may display no symptoms of the disease.

The child may be born dead, or alive with abundant evidence of syphilis, or apparently healthy, the lesions not appearing for several weeks.

Much the same organs are involved as in the acquired form, namely the skin and mucous membranes, the bones, the viscera, and the eye and ear. The lesions also are similar except that the diffuse inflammatory infiltration of parenchymatous organs is very much in evidence. The child shows no primary lesion, for that occurs in the placenta.

The *skin* is the seat of a variety of eruptions, varying from rose- or copper-colored spots to vesicular or even pustular forms. The buttocks, the neighborhood of the anus, the angles of the mouth, and the palms of the hands and soles of the feet are favorite sites. Lesions in the last-named position are scaly in type with much desquamation. The lesions around the mouth leave pale radiating scars from which a diagnosis may be made in future years. The whole skin may be dry and wrinkled giving to the child a prematurely old and wizened appearance.

Mucous Membranes.—Inflammatory lesions similar to those of acquired syphilis are common. One of the earliest symptoms is due to inflammation and ulceration of the mucous membrane of the nose, giving rise to the difficulty in breathing known as "snuffles." The diarrhea frequently present is probably due to a similar condition in the intestine.

The Bones.—Two chief types of lesions are met with, the atrophic and the productive; the former are rare, the latter common.

In the *skull* there may be atrophy of the cranial bones at the points of greatest pressure with marked thinning, giving rise to the same condition of "craniotabes" as is found in rickets. The productive form is dependent on a syphilitic periostitis, affects the frontal and parietal bones close to the middle line in the region of the anterior fontanelle in a remarkably symmetrical manner, and gives rise to the formation of rounded bosses of bone, sometimes as much as half an inch in thickness, of highly characteristic appearance.

The *long bones* may be the site of productive changes giving rise to the formation of gummata and osteophytes, or there may be a fairly uniform thickening of part of the bone from periosteal activity, often altering the contour as in the sabre-shaped tibia. Atrophic lesions may occur at the epiphyseal ends of the bones, accompanied by absorption of the bone and separation of the epiphysis.

The *teeth* show characteristic changes; not the milk but the permanent teeth. The typical teeth, known as "Hutchinson's teeth" after Sir Jonathan Hutchinson who was the first to describe them accurately,

are small and ill-developed, more widely spaced than normal, narrower at the apex than at the base so as to appear peg-shaped, and usually display a central notch. The teeth principally affected are the upper central incisors. It is now known that the six-year molars are affected in congenital syphilis much more regularly than are the central incisors, and in even more characteristic fashion. The grinding surface is eroded, and the greater part of the surface of the molar becomes pitted, excavated, and discolored. The condition has been called the "honey-combed molar of hereditary syphilis."

The Eye.—About the age of puberty an interstitial keratitis often develops, affecting first one eye and then the other, and producing a ground-glass opacity, which usually clears up to a great extent, leaving only a few opaque patches.

The Ear.—Quite early in the disease a marked degree of deafness may develop, which is apparently central in origin. The middle ear may also be the seat of syphilitic inflammation.

Many features of the disease are summarized in this passage from Hutchinson's original paper (1861) in which he described the lesions of the teeth which bear his name. "The subjects of inherited syphilis show, in nine cases out of ten, a very pasty pallid skin, and a drawn, haggard expression of face, as of premature old age. The bridge of the nose is almost always sunken and broad, and there are frequent little pits or cicatrices about the checks and forehead and symmetrical linear scars extending from the angles of the mouth. This patient has also suffered from interstitial keratitis, which has left both her corneas hazy; whilst both pupils are notched and irregular, from the effects of a bygone attack of iritis."

ACTINOMYCOSIS

Actinomycosis belongs to the group of the infective granulomata, but the lesions are complicated by suppuration. It is caused by the actinomyces or ray fungus, which belongs to the group of the Streptothriceae.

Bacteriology.—The actinomyces grows in the tissues in the form of little clumps or colonies, which are easily seen in the pus by the naked eye. These clumps are of a yellow color, and constitute the well-known "sulphur grain" bodies. When one of these bodies is crushed under a cover glass and examined unstained, two elements may be distinguished, branching mycelial filaments and club forms. The filaments constitute the greater part of the body. In the center they form a dense felted mass. The clubs are pear-shaped bodies which form a fringe round the periphery of the colony. They probably represent a means of defense against the protective forces of the tissues. The filaments are Gram-positive, the clubs are Gram-negative. There are several types of actinomyces, some aerobic, others anaerobic. Most of the aerobic varieties are saprophytic and cannot be made to infect animals or man, but a small group is pathogenic. The great majority of human and animal infections are due to anaerobes.

The disease is common in cattle, occasionally affects horses, and is regarded as being rare in man. It is more than probable, however, as Cope points out in his excellent monograph that the principal reason

for the apparent rarity in man is the frequency with which the diagnosis is overlooked. The disease may occur in the most unlikely situations and in the most atypical forms. Actinomycosis should always be considered in the diagnosis in the case of any newly formed subacute or chronic swelling, whether it appear neoplastic or inflammatory in nature, in the region of the mouth, face, neck, thorax, or right side of the abdomen.

The method of infection is still open to doubt. Direct transmission from an infected animal to man has never been proved. The commonly accepted view that infection is acquired through the eating of infected grain has little to support it, for the Actinomyces bovis has never been demonstrated on grasses and grains, although other micro-organisms with somewhat similar characters have been described in these positions. Trauma produced by vegetable matter may aid the entry of the pathogens, and by inducing anaerobic conditions may assist their growth in the tissues. Secondary invasion by pyogenic organisms is common, and the resulting suppuration may reduce the oxygen tension in the tissues and favor even more the growth of anaerobic actinomyces. It appears probable, as J. H. Wright originally suggested, that the organism of actinomycosis is a true parasite and not a saprophyte, that it normally inhabits the alimentary canal, and that is enters the tissues through wounds, carious teeth, etc. The common portal of entry is therefore the alimentary canal, occasionally the fungus is inhaled, and in some cases infection enters through the broken skin. A carious tooth is often the center of the lesion, because the unhealthy gums adjacent to such teeth are readily injured and infected. Lord produced granulomatous lesions in guinea-pigs by inoculating them with scrapings from carious teeth and from the crypts of tonsils of persons free from actinomycosis, and these lesions contained granules composed of filaments and clubs apparently identical with those seen in actinomycosis. On the other hand all attempts to convey infection from human lesions to animals have been attended by failure. Cope remarks that the site in the mucosa through which the organism enters is seldom discernible. When once penetration has occurred the wound of entry heals promptly, and the pathological process works away from the mouth, intestine or rectum as the case may be.

The sites of infection are four in number. About 60 per cent of cases occur in the head and neck, 20 per cent in the gastro-intestinal canal—usually the region of the cecum and appendix—15 per cent in the lungs, and the remainder in the skin. In the cow the jaw is chiefly affected, a condition known as "lumpy jaw"; the tongue may be much enlarged and very firm, a condition of "woody tongue." Most of the cases in man originate in the mouth and pharynx, often in relation to carious teeth.

The streptothrix of actinomycosis exhibits some remarkable peculiarities in its method of spread which distinguish it from tuberculosis and syphilis, two conditions with which it is readily confused. Starting in the connective tissues, such as the subcutaneous, the submucous, the subperitoneal, and the subpleural, it extends by direct continuity. Apparently this extension occurs through some of the filaments being carried into the surrounding tissues, although by what means is at present unknown. Spread by the blood stream is uncommon, but a lesion may rupture into a vessel and give rise to metastases in distant organs. The

liver, the brain, and the heart may thus be involved, and in rare cases the kidney, spleen, and ovary. Spread by the lymph stream is practically unknown, and the entire lymphatic system appears to enjoy a surprising degree of immunity, thus differing most markedly from its behavior in tuberculosis.

The lesions are similar to those of such granulomata as tuberculosis and syphilis, between which it is sometimes very difficult to draw a distinction. A firm mass slowly develops, which may retain its firmness for a long period, but finally softens and breaks down. The connective tissue, the muscle, and the bone are successively destroyed and replaced by granulation tissue which becomes riddled with abscesses. An abundant fibrous tissue reaction may lead to a brawny induration of the neck which

Fig. 28.—Actinomycosis. (Jacobi.)

may closely resemble sarcoma. The overlying skin becomes red and edematous, and may be perforated by the openings of numerous sinuses (Fig. 28).

The pus is usually thin, and may contain the tiny yellow "sulphur granules," no longer than a grain of mustard, from which alone an absolute diagnosis can be made. These granules are most readily found in the pus of a newly opened lesion. When the lesion has been discharging for some time it may be impossible to demonstrate them. In such cases it is best to allow a considerable amount of secretion to collect before examining it. The grains consist of a felted mass of mycelial threads at the periphery of which the peculiar club-like bodies can usually be recognized. The clubs are only found in the body, never being present in cultures.

In the *abdominal form,* which usually originates in the cecum or appendix, the chief growth is in the submucosa, in which flat gray nodules appear. In the course of time a large firm mass is formed, readily mistaken for malignant disease, and eventually suppuration converts the mass into a nest of abscesses. The abdominal wall may become involved, and a sinus discharges on the surface. The liver may become infected either by direct extension or by spread via the portal vein. A large honey-combed mass is formed which resembles a sponge saturated with pus.

The *lungs* are involved by extension downwards from the neck or upwards from the abdomen, although in some cases the infection appears to originate in a bronchus. The disease follows its usual course, so that the lung becomes riddled with abscess cavities, usually small and surrounded by abundant fibrous tissue. The condition may closely simulate
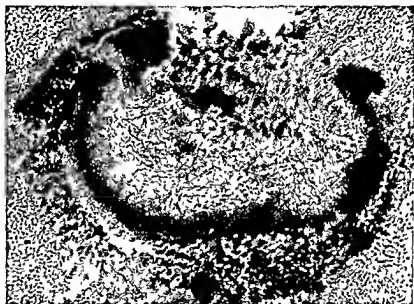
Fig 29.—Section of tissue in actinomycosis. Large numbers of branching mycelia. × 275

tuberculosis, but as a rule the lower rather than the upper lobes are involved.

The microscopic appearance is that of a granuloma in which *suppuration* is frequently a prominent feature. The picture naturally varies much depending on whether suppuration has or has not set in. If the examiner is unusually fortunate he may find the masses of radially arranged branching mycelial filaments (Fig. 29), around which is seen the usual collection of small round cells and mononuclears, whilst further out a well-marked fibroblastic reaction is evident. Giant cells may be present. Failure to find the mycelium in sections of the tissue is so frequent that it should never be accepted as a point of diagnostic value. For the same reason it is a mistake to excise a piece of the hard tissue with a view to an examination for mycelia. When softening occurs they will be found infinitely more easily in the pus.

A word as to examining for the granules. The person with the best opportunity for finding them is the surgeon who opens the abscess. It is much better to pick out the granules and send them to the laboratory than to send a sample of pus taken at random. In the laboratory a good method is that advised by Colebrook. A few drops of pus are collected in a test-tube half full of water and fitted with a cork. The tube is shaken vigorously; the elements of ordinary pus are emulsified, whereas the sulphur granules are not broken up, sink to the bottom of the tube, and are easily recognized when the tube is held up to the light. A granule is transferred to a slide by means of a capillary pipette, lightly crushed under a cover glass, and examined unstained. The ray formation of clubs is seen between the surrounding pus cells and the core of the granule.

The course is very similar in whatever part of the body it occurs. First there is a firm tumefaction with no evidence of inflammation, then areas of softening appear, and eventually the part may be riddled with sinuses. In the lower jaw the disease causes a brawny swelling which may extend down the neck, sometimes apparently severing its connection with the mandible. Abscess formation will probably occur sooner or later. Spread by the portal vein may lead to the formation of large, honey-combed masses in the liver, which may still further suggest the possibility of carcinoma. General symptoms of infection such as anemia, wasting, or fever, may be present in the later stages.

SPOROTRICHOSIS

During recent years a large number of cases of granulomatous infections caused by pathogenic fungi have been described, particularly in the United States. Of these two of the most important are sporotrichosis and blastomycosis.

Sporotrichosis is a chronic infection produced by a fungus of the genus Sporotrichium. The first case was described by Schenck in America in 1898. The fungus enters the skin through some abrasion and sets up a slow inflammation which manifests itself in a series of gumma-like bodies, which break down to form abscesses, and these in turn may discharge on the skin as ulcers.

The *clinical differentiation* between this condition and syphilis or *tuberculosis is often difficult and may be impossible*. There is, however, something peculiarly suggestive about the gradual march of the disease up a limb along the line of the lymphatics, with here and there the development of a granulomatous mass. The fact that the disease responds well to iodide of potassium increases the confusion between it and syphilis.

Histological examination of the lesion is of no assistance. The picture is one of granulation tissue composed of fibroblasts, lymphocytes, epithelial cells, and giant cells. The latter are supposed to be characteristic, but in a typical case which I studied there were none present. Much, of course, will depend upon the stage at which the lesion is examined. When necrosis and suppuration set in the picture will be much changed.

The only certain method of diagnosis is by *bacteriological examination* of the discharge from the lesions. The elongated spores of the fungus itself will not be found in human lesions, but a culture can readily be made upon ordinary agar, although a sugar-containing medium is even

better. As the fungus grows well at room temperature, the whole procedure can easily be carried out by a practitioner with a taste for bacteriology. The appearance in the course of a few days of a wrinkled pellicle which gradually darkens in color until it becomes black will prove an ample reward.

BLASTOMYCOSIS

Fig. 30.—Skin lesion in blastomycosis

Another inflammatory condition, at first granulomatous but later suppurative, is caused by the yeast-like fungi known as the blastomycetes. The organisms, unlike the case of sporotrichosis, are found in the pus of the lesions. They are spherical bodies, somewhat larger than a red blood corpuscle, and present two characteristic features: (1) each organism is surrounded by a clear double contour (Fig. 31), and (2) many of the organisms, like true yeast cells, show budding. The blastomycetes are best demonstrated by placing some of the pus on a slide, adding a drop of 10 per cent caustic soda, and examining the specimen unstained.
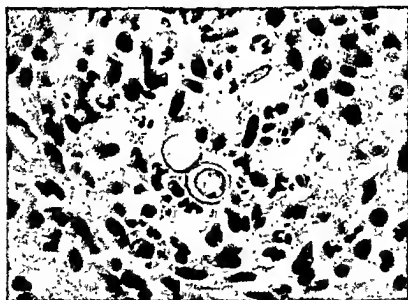
Fig. 31.—Blastomycosis. The suppurative element is marked. Two blastomycetes are seen, one of which has a double contour. × 600.

The lesions are usually confined to the skin, so that the condition is often known as blastomycetic dermatitis. They frequently follow a slight wound. At first they appear as papules, and throughout the disease the lesions are usually papillomatous in some part (Fig. 30). In time they

break down, become pustular, and ulcerate. The disease progresses over the skin, but as one part advances another part may heal. In this way large areas may in time be involved. The diagnosis from tuberculosis and syphilis is again often a matter of great difficulty, and has to depend on a demonstration in the pus of the infecting fungus. In some cases the fungus can be grown from the pus with considerable readiness on ordinary media at room temperature, but the demonstration of the spherical bodies in direct smears is the more satisfactory.

The microscopic appearance varies with the stage of the disease. In the early stage the picture is that of tuberculous granulation tissue with numerous giant cells, but later suppuration becomes quite marked (Fig. 31). A noteworthy feature is the evidence of considerable epithelial hyperplasia of the epidermis with downgrowths readily mistaken for carcinoma.

Occasionally it happens that the disease does not remain confined to the skin but invades the *internal organs.* As long as it is confined to the skin it is not dangerous to life, although of long duration. When it becomes generalized the termination is almost always fatal. It is by no means certain that the generalized condition is the same disease or caused by the same organism as the local one, but for a discussion of this problem treatises on bacteriology must be consulted.

The organs most frequently involved are the lungs, the muscles, and the bones, but almost any organ may be attacked, and one writer has described a case of blastomycosis of the brain. The pulmonary lesions are the first to attract attention, and the association of a skin affection with chronic pulmonary disease should suggest a search in the sputum for blastomyces. The lesions in the lungs resemble bronchopneumonia or miliary tuberculosis, but cavity formation is uncommon. In bones the usual lesion is a suppurative osteomyelitis developing at the end of one of the long bones. Occasionally the vertebral column is affected.

In the generalized cases the micro-organisms are usually present in large numbers, and they are three or four times the size of those seen in the skin lesions. The histological picture in the internal organs is a combination of the granuloma formation and suppuration already described in the case of the skin.

LYMPHOGRANULOMA VENEREUM

The common name of this condition is lymphogranuloma inguinale, but it is so readily confused with granuloma inguinale that the more accurate term lymphogranuloma venereum is preferable. It is a venereal disease caused by a filtrable virus, the primary lesion being on the glans or vulva, but often so insignificant that it may never be noticed. The infection spreads by the regional lymphatics, but as the distribution is different in the two sexes, the resulting secondary lesions are correspondingly different. In the male the inguinal lymph nodes become enlarged after a few weeks, indurated and painful. Softening and suppuration follows, the result being an ulcer of considerable size and sinuses which refuse to heal for a long time. In the female the lymphatics from the vagina pass mainly to the lymph nodes around the rectum, so that there is a chronic inflammation of the perirectal tissues which may result in

an anorectal stricture (Fig. 32). Obstruction to the deep lymphatics may also lead to elephantiasis of the labia with ulceration, the condition known as *esthiomene*. Any one of these three conditions, inguinal granuloma, rectal stricture and esthiomene, may occur independently and used to be regarded as different diseases. The Frei test first showed that they were manifestations of a single disease, and subsequently the virus has been isolated from each type. Distant lesions have been reported in the colon, brain, etc.

The *microscopic* picture in the inguinal lesions is that of irregular star-shaped abscesses bordered by a palisading of epithelioid cells and occasional giant cells (Fig. 33); plasma cells are very numerous in the surrounding tissue. It may be mistaken for tuberculosis. In esthiomene and rectal lesions the picture is non-specific. Further details will be found in the extensive review by D'Aunoy and von Haam. The disease is commoner in the Negro, but may occur in the white. The diagnosis is confirmed by the Frei-Hoffmann allergic skin reaction which results when the inactivated virus is injected into the skin.

Granuloma inguinale is a chronic inflammatory lesion of the genital and anal regions practically confined to the Negro, of uncertain etiology, and characterized by the presence of intracellular rod-like structures known as Donovan bodies and by occasional very large mononuclear cells with spaces in the cytoplasm. The lesions respond readily to intravenous injections of tartar emetic.

Lycopodium Granuloma.—A granulomatous reaction may occur as the result of a non-living irritant, and, as in the case of silica particles and lycopodium powder, the microscopic picture may resemble that of tuberculosis. Lycopodium powder, used for dusting surgical gloves, consists of the spores of the club moss, Lycopodium clavatum. The spores are killed during the process of sterilization, so that the reaction is a foreign body one to the dead particles imbedded in the tissues. The lesion consists of epithelioid cells, multinucleated giant cells, lymphocytes, and fibroblasts with areas of necrosis (Fig. 34). The spores may be found in the granulation tissue, the areas of necrosis, or the giant cells. They are large structures, measuring 30 microns in diameter, and as they stain very poorly with hematoxylin and eosin they are easily overlooked in routine sections. In Ziehl-Neelsen preparations they stain a brilliant red. In tissues the granuloma will form a mass; on the peritoneum the result may be tubercle-

Fig. 32.—Fibrous rectal stricture in lymphogranuloma venereum.

like nodules or adhesions. A similar reaction is produced by talcum powder, the irritant in this instance being talc crystals, which can be recog-

Fig. 33.—Lymphogranuloma venereum, showing epithelioid and giant cells. X 120.

Fig. 34.—Lycopodium granuloma. X 75

nized since they are doubly refractive under Nicol prisms. Here again a tumor-like mass may slowly develop.

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CHAPTER V

SPECIAL WOUND INFECTIONS

ERYSIPELAS

Erysipelas is an acute inflammation of the lymphatics of the skin or a mucous membrane due to the entrance of Streptococcus pyogenes through a wound. This wound may be so minute as to escape notice, but a break in the surface is always present.

The disease is due to a special variety of streptococcus. Birkhaug, in a study of the biology of the hemolytic streptococci isolated from cases of erysipelas, found that these organisms could be differentiated by means of immunological methods from the scarlatinal strains and from a large series of miscellaneous hemolytic streptococci.

In 90 per cent of cases the face or scalp is the site of the inflammation. It is probable that in very many of these cases the starting point is a latent infection of the nose or nasal sinuses. It may follow operations which lay open a diseased middle ear or mastoid cells. In the remaining cases the leg or foot is generally affected. In the newly-born the umbilical cord may be infected. The mucous membrane of the mouth or of the vagina may occasionally be involved. The relation of erysipelas to puerperal fever is well recognized.

Some persons are liable to recurring attacks of erysipelas, showing that the factor of the patient is of importance as well as the factor of the bacteria. On the other hand it not infrequently happens that an attack of erysipelas is followed by the improvement or recovery of a morbid condition from which the patient may have suffered for a long time. Such conditions are chronic eczema, old ulcers of the leg, and even innocent and malignant tumors. It is on this fact that the use of Coley's fluid, which contains the toxins of the streptococci of erysipelas, is based.

Erysipelas used to be regarded as an extremely infectious condition. The infectivity, however, depends entirely on the presence of a discharge containing the casual bacteria. If the skin is unbroken there is no danger of infection.

Morbid Anatomy.—The disease spreads from the site of inoculation as a drop of grease spreads on a piece of paper. The advancing margin is of a bright or dull red color, and slightly raised above the general surface. The margin itself is irregular in outline, and has been aptly likened to the burnt edge of a smouldering sheet of paper. Just beyond the sharp margin the lymphatics are crowded with streptococci. The margin itself shows acute congestion and the lymph spaces of the corium are crowded with cells. The inflammatory cells are mainly lymphocytes and wandering mononuclear cells. It is certainly remarkable that whereas in ordinary streptococcal infections the characteristic defense cell is the polymorphonuclear leucocyte, in erysipelas the cellular exudate should be mainly composed of small mononuclears. The center of the patch may show

ism a very characteristic appearance. They are several times the diameter of the bacillus, and as they are terminally situated they give it the appearance of a drumstick. The bacilli possess flagella, but are only feebly motile. In smears of pus from an infected wound some of the organisms may possess spores, but many may not, and appear merely as slender rods.

The tetanus bacillus will only grow under anaerobic conditions, but may be cultured on ordinary media under these conditions. The task of separating it from accompanying organisms is facilitated by taking advantage of the heat-resisting property of its spores. A mixed culture is grown and is then heated to 80° C. for an hour. At this temperature the non-spore bearers are killed, and B. tetani can be obtained in pure culture.

The bacillus being a strict anaerobe, its growth is greatly favored by the presence of other aerobic bacteria, so that it is never found in pure culture in a wound. Large, lacerated, infected wounds, plentifully contaminated with earth, are those which are liable to be the starting point of tetanus. Occasionally the break in the surface may be a mere scratch or pin-prick. It must be borne in mind that the presence of tetanus bacilli or spores in the tissues is not sufficient in itself to produce the disease. The bacilli were frequently found in the wounds of soldiers who never developed any symptoms of tetanus. Tetanus is not merely a wound infection, but an infection of septic wounds.

In examining catgut for tetanus certain points must be kept in mind. The catgut used in surgical operations consists of the submucous layer of the small intestine of lambs. This is twisted tightly into strands, so that any tetanus bacilli which may be included are extremely well protected. Simple culture of such infected material may quite fail to demonstrate the presence of the bacilli. This can best be done by macerating the catgut or by implanting it in the tissues of a guinea pig. By this means the imprisoned bacilli are liberated, and may be recognized either by their growth on artificial media or by their biological effect on the guinea pig. It must be remembered that the necrotic material surrounding a piece of catgut in a case of post-operative tetanus may produce no effect when injected into an animal, but that the bacilli may be demonstrated in the catgut by the above-mentioned methods.

The symptoms of the disease need not be fully described here. They are due essentially to such a degree of sensitization of the motor apparatus that an extreme hypertonicity is produced, and the sensitive reflex arc reacts so readily that clonic spasms may result from the most trifling stimuli such as a breath of cold air, a light touch, the banging of a door, or even the act of swallowing. The whole motor system is in an explosive condition, and the explosions are terrible in their intensity.

Stiffness of the muscles of mastication, notably the masseters, producing a condition of "lock-jaw" is first noticed by the patient. The muscles of the neck, particularly the sternomastoid and trapezius, then share in the tonic contraction followed by the muscles of respiration, the diaphragm, and lastly the muscles of the limbs. Clonic spasms of increasing severity are superadded to the general condition of tonus. The patient may die in one of these spasms, or death may be due to asphyxia produced by the vise-like grip of the muscles of respiration.

The clinical picture of tetanus called forth long ago these remarks by

Aretaeus the Cappadocian: "An inhuman calamity! an unseemly sight!
a spectacle painful even to the beholder! an incurable malady! owing to
the distortion, not to be recognized by the dearest friends; and hence the
prayer of the spectators, which formerly would have been reckoned not
pious, now becomes good, that the patient may depart from life, as being
a deliverance from the pains and unseemingly evils attendant on it."

Local tetanus was frequently seen during World War I in men who had
received a prophylactic injection of antitoxin. General tetanus failed
to develop, but the muscles of the affected part became hypertonic, and
in some instances clonic spasms appeared. It may be accounted for by
Abel's suggestion that the toxin may act locally on striated muscle in
addition to the general effect due to lymphatic absorption and blood
dissemination.

ANTHRAX

Anthrax is an infectious disease common in herbivorous animals such
as horses, cattle, and goats, and occasionally attacking man. Man may
become infected in three ways: (1)
through the skin (malignant pustule),
(2) through the respiratory tract
(wool-sorters' disease), and (3) through
the alimentary canal. The only form
of interest to the surgeon is the
wound infection which gives rise to
malignant pustule.

Animals vary greatly in their sen-
sibility to anthrax. Mice, rabbits, and
guinea pigs are so susceptible that in
them the disease is of a most fatal
nature, practically invariably devel-
oping into a septicemia in which the
blood and every organ in the body
comes to swarm with anthrax bacilli.
Enlargement of the spleen is so con-
stant in susceptible animals that the
disease is known as splenic fever.
Pigeons, fowls, and rats, on the other
hand, show a high degree of immunity,
although that immunity may be bro-

Fig. 35.—Anthrax: malignant pustule
(Jacobi.)

ken down by adverse conditions. Man occupies an intermediate position,
for in him the skin lesion may remain localized, or again a condition of
general anthrax septicemia may develop. In the first case the prognosis is
good, in the second it is usually regarded as hopeless.

The most important characteristic of the bacilli is their tendency to
form spores outside of the body. The fact that no spores are formed
within the body is of the greatest importance in indicating the means of
disposal of the dead body of an animal suffering from the disease. If no
blood is shed the ground in which the animal is buried soon becomes
innocuous; if it is, the spores may lurk in the soil for many years, and
form a constant menace to other animals.

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material should be injected into the peritoneal cavity of a male guinea pig. In a remarkably short time, usually within 24 hours, a characteristic acute inflammation of the tunica vaginalis is set up. This is known as the Strauss reaction. The fluid from the tunica is inoculated on potato, where it produces a transparent growth which by the end of the third day has a yellowish honey-like appearance. The reaction on potato, together with the other characters already described, is pathognomonic of glanders.

Infection from the nasal discharge of a diseased horse occurs through a break in the skin of an exposed part such as the face or hand, or first involves the mucous membrane of the nose or mouth.

The microscopic appearance of the primary and also of the secondary lesions is in no way characteristic, being merely that of one of the infective granulomata, although without the distinguishing features of tuberculosis or syphilis. In the more acute lesions the picture may be that of ordinary suppuration. The specific micro-organism may be found in the discharge, although seldom in large numbers.

After an incubation period varying from a few days to two or three weeks a papule appears which soon develops into a pustule. A crop of pustules forms which may be mistaken for anything from boils to smallpox. At a later stage the chief skin lesions may be large irregular ulcers discharging a foul blood-stained fluid. When the infection is in the nose the ulceration may involve the bones of the face.

The disease may run an acute or a chronic course. The *acute form*, which is invariably fatal both in horses and man, is characterized by a rapid spread of the surface infection, the formation of metastatic nodules and abscesses in the lungs, liver, spleen, and kidneys, and the development of the general symptoms of septicemia and pyemia.

In the *chronic form* the manifestations are protean, and the diagnosis often a matter of great difficulty. A nodular thickening of the lymphatics is very characteristic, especially in horses, and to this condition the term *farcy buds* is applied. Farcy is the name given to the chronic form as seen in the horse. The neighboring glands become swollen, and in addition to widespread ulceration there may be secondary deposits in the subcutaneous tissues and in the muscles. Indeed it may be said that glanders is a disease of lymphoid tissue, of connective tissue, and of muscle. In the only case which I have seen the destruction of the muscles of the leg was extreme, so that sinuses 6 or 8 inches in length were formed, but neither bones nor joints were involved.

The course of the disease may last for months or even for years. Anyone wishing to read a thrilling and dramatic description of an attack of glanders should consult two articles by S. H. Gaiger describing the course of the disease in his own person, and published in the *Journal of Comparative Pathology*, 1913 and 1916. The first attack of the disease lasted for two years and a quarter, the second for a year and three quarters. In all, 82 operations had to be performed. Gaiger emphasizes the fact that in a pure glanders infection the bones are not attacked. It was only when a mixed infection with staphylococci developed that his bones and joints became involved. These two papers contain many useful suggestions regarding treatment. This is a striking example of recovery after a most severe infection, but the majority of cases eventually end fatally.

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HEMORRHAGE, THROMBOSIS, AND EMBOLISM

HEMORRHAGE

Hemorrhage may be due to three main groups of causes: (1) trauma, (2) pathological changes in the walls of the vessel, and (3) certain constitutional conditions.

It is the traumatic variety with which the surgeon is principally concerned.

The pathological changes in the walls may be patches of atheroma leading to cerebral hemorrhage; the lodgment of bacteria in the lumen of minute vessels causing weakening of the wall and it may be the formation of a mycotic aneurism with subsequent rupture; or the action of toxins upon the inner coat.

The constitutional group is the most obscure. Doubtless in such conditions as Banti's disease and leukemia there is in addition a local change in the vessel wall. In such conditions, however, as hemophilia, vicarious menstruation, etc., a local cause is hardly to be looked for.

The hemorrhage may be *external* upon the surface, or *internal* into the tissues. Internal hemorrhage may follow laceration of a vessel from trauma, and a large amount of blood may be poured into the tissues of a limb. The part becomes very dusky and swollen, and the circulation is interfered with so seriously through pressure on the veins that there may be danger of gangrene.

Hemorrhage is divided by the surgeon into primary and secondary. *Primary* hemorrhage occurs at the time of injury to the vessel. *Secondary* hemorrhage occurs at some later date, and is due to interference with the mechanism for the arrest of the hemorrhage. Such interference is usually due to bacterial infection.

The proteolytic ferments produced by the bacteria soften the newly-formed coagulum, and allow the hemorrhage to occur afresh. Secondary hemorrhage is rare in civilian work, but is very common in war wounds. From the pathological standpoint, however, the two conditions are identical.

The Arrest of Hemorrhage.—The temporary arrest of the hemorrhage is brought about by the formation of a clot, due to the coagulation of the blood. The *permanent* arrest is accomplished by the formation of an inflammatory exudate which in due time becomes firmly organized and seals the vessel.

Many secondary factors come into play, but it must be remembered that these are merely adjuvants to the essential phenomenon of coagulation, without which they are useless and without meaning. Of these secondary factors the more important are as follows.

1. When an artery is cut or still better when it is torn across, two

phenomena occur, retraction and contraction. There is a large amount of elastic tissue in the inner coat and a certain amount in the middle coat of the smaller arteries. The recoil of this divided elastic tissue produces retraction of the inner and middle coats, so that these are drawn within the outer coat and the surrounding tissues, which thus form a sheath for the divided end of the vessel. The inner coat contains so much elastic tissue that it curls back into the lumen of the artery, sometimes completely blocking it. This mechanism is unable to come into play when an artery is only partially divided, under which circumstances it is best to make the division complete. A properly applied ligature acts in the same way; the inner and middle coats are ruptured and retract, and the constricted outer coat then closes the lumen.

2. If the hemorrhage is sudden and severe there will be a great fall in blood-pressure, due to anemia of the vaso-motor center in the medulla. Such a fall will naturally facilitate the formation of an occluding clot in the vessel. The use of stimulants which will raise pressure and wash away the clot is therefore to be avoided.

3. To compensate for the loss of fluid in the vessels there is a great flow of lymph into the blood stream, partly from the lymphatics, partly from the tissue spaces. This favors the conversion of fibrinogen into fibrin, and therefore renders the blood more readily coagulable.

Clotting or Coagulation of Blood.—A clear distinction must be drawn between blood clotting and thrombosis. Clotting which occurs when blood is shed from a vessel, and especially when it comes in contact with injured cells, consists in the formation of a network of fibrin, in which are entangled various blood cells. This happens when blood is collected in a test-tube, unless some anticoagulant is added. Thrombosis occurs in the streaming blood, *i.e.,* in vessels or heart, and consists in the formation of a solid mass of platelets. When blood clots, fibrin is formed by the action of a ferment, *thrombin*, on *fibrinogen*. The thrombin in turn is formed by the interaction of *prothrombin* with *calcium salts*. Prothrombin is prevented from uniting with calcium under normal conditions by the action of *antithrombin*. The antithrombin may be neutralized by *thromboplastin* (*thrombokinase*) which is liberated as the result of injury either to tissue cells or platelets.

Heparin is a substance concerned with the control of blood clotting which is of great importance to the surgeon. It is an anticoagulant of extreme potency, which was first obtained in Howell's laboratory in 1916 from an extract of liver (hence its name). Nearly twenty years elapsed before a purified form was produced in adequate quantities from beef lung and liver by Best and his associates in Toronto. Tissues which stain metachromatically with toluidin blue are rich in heparin, and this is especially true of mast cells (Jorpes). These cells may be an important source (or depot) of heparin in the body. It is present in subintimal tissues of arteries and in subpleural and subperitoneal connective tissue; these tissues can thus liberate heparin at sites liable to fibrin formation. Heparin has a twofold action. (1) When added to blood it completely prevents clotting by preventing the union of prothrombin with calcium salts. Heparin, indeed, appears to be practically identical with antithrombin. The result is a prolonged clotting but normal bleeding time, *i. e.,* the

picture of hemophilia. (2) It prevents thrombosis by interfering with the agglutination of blood platelets. Murray of Toronto has demonstrated convincingly the great value of the intravenous administration of heparin in blood vessel surgery with the object of preventing thrombosis.

It has been recognized for many years that "sweet clover disease" in cattle is characterized by a tendency to hemorrhage, sometimes fatal. The disease arises from eating *improperly cured* hay or silage made from sweet clover. Link and his associates at the University of Wisconsin have succeeded in isolating the active hemorrhagic agent from spoiled clover, and finally in synthetizing it. Chemically it is 3,3¹-methylene-bis-(4-hydroxycoumarin), known more briefly as *cumarin*. Butt and his colleagues have studied the effect of the hemorrhagic agent, and find that it closely resembles heparin in prolonging the coagulation time, but it has the advantage that the action is much more prolonged and that it can be taken by mouth instead of being injected intravenously.

Vitamin K, the coagulation vitamin, is another link, although an indirect one, in the complex process of coagulation. In 1930 Dam of Copenhagen observed that chickens fed on a deficient diet developed a hemorrhagic tendency. Within a short time the responsible factor was isolated, crystallized, and finally synthetized; it was named vitamin K (koagulationsvitamin). In animals showing the hemorrhage tendency, the prothrombin was found to be low, because vitamin K is necessary for its formation. In man the deficiency of the vitamin is more likely to be due to lack of absorption than to inadequate supply in the food. The vitamin is not absorbed from the bowel unless bile is present. In obstructive jaundice there is absence of bile in the bowel, low plasma prothrombin, and increased clotting time with a tendency to hemorrhage. This explains the well-known tendency to post-operative bleeding in cases of obstructive jaundice. It can be corrected by administering vitamin K and bile, or by using the synthetic vitamin which does not require bile for its absorption. If the liver is extensively diseased (amyloid, advanced cirrhosis, etc.), no form of the vitamin is of use, because the damaged liver is unable to form prothrombin. Continued intracranial hemorrhage in the new-born is due to low plasma prothrombin, caused in turn by vitamin K deficiency. Much of the vitamin is produced by intestinal bacteria, and during the first few days of life the bowel is devoid of bacteria; hence the tendency to hemorrhage.

But although the clotting of blood is brought about by this delicate and ingenious mechanism, it does not constitute the only, or indeed the most important, means by which the hemorrhage is arrested. It plays an essential part in the formation of the temporary clot, but of only one variety of that clot, and it by no means the most important.

Two varieties of *temporary clot* are to be distinguished, the red and the white. The *red clot* is formed both outside and within the lumen of the vessel, and is the result of the process just described. It therefore consists almost entirely of fibrin containing red cells in the meshes of its network together with a few leucocytes. It is soft and jelly-like, and would never of itself be capable of effectively arresting the hemorrhage. It plays the part of a buffer, which serves to slow the flow of the blood, and thus allow of the formation of the much more efficient white clot.

The *white clot* is entirely different both in formation and composition. While the red clot is composed mainly of fibrin, the white clot consists almost entirely of blood platelets, with an admixture of a little fibrin and a few leucocytes. It is, in short, a thrombus. As the blood stream slows down the platelets fall out of the main current, and adhere to the injured end of the vessel, where they form a sticky white mass which acts as an effective cement to seal the injured vessel. This white clot formation, brought about by the conglutination of the platelets, is a more fundamental and primitive process than the formation of the red clot. It is found as a response to vascular injury throughout the animal kingdom, whereas it is only in the higher vertebrates that the chemical formation of fibrin plays any part in the process of clot formation.

The temporary clot is now completed, and may be compared to a long nail the head of which, formed mainly by the white clot but partly by the red, closes the end of the vessel, whilst the stem, represented by the red clot, occupies the lumen and may extend up the vessel to the nearest collateral.

The *permanent clot* is formed as the result of a process of plastic inflammation which commences shortly after the injury to the vessel. At the cut end of the vessel there occur those phenomena which have already been studied in our review of inflammation. An inflammatory exudate consisting mainly of lymph is formed, and soon becomes converted into granulation tissue by the ingrowth of new capillaries and fibroblasts. The temporary clot becomes vascularized and fibrosed in the same way, but shrinks considerably in the process, so that the internal clot may be represented merely by a thin fibrous cord. By this time, however, the end of the vessel is securely plugged by a mass of fibrous tissue, and the buffer action of the temporary clot is no longer required.

A *post-mortem clot* is seen typically in the heart after death. It is red, soft, friable, and is not attached to the heart wall. In many cases, however, although the lower part of the clot presents these characters, the upper layers may be tough and elastic, yellow in color, and of a translucent appearance. This is the so-called chicken-fat clot. The explanation of the appearance is simple. If clotting is delayed for some time after the circulation ceases the red cells will gradually settle to the bottom of the clot, where they form the ordinary red clot, whilst the supernatant plasma coagulates to form the pale chicken-fat clot.

THROMBOSIS

Thrombosis occurs when the blood is actually flowing. The essential factor in thrombosis is an agglutination of the blood platelets, which adhere together at the point of formation of the thrombus and form ridges running at right angles to the flow of the stream. The surface of these ridges becomes thickly plastered with leucocytes. Moreover the platelets appear to liberate thromboplastin, whereby the neighboring fibrinogen is converted into fibrin which hangs in festoons between the ridges of platelets, entangling incidentally large numbers of red blood cells as they flow by.

A fresh thrombus, therefore, is made up of an essential basis of platelets, with the addition in varying degrees of fibrin, leucocytes, and red

blood cells (Fig. 36). Disintegration of these various elements soon occurs, so that they come to form a homogeneous whole. The red cells lose their hemoglobin, and the color of the clot changes from red to yellowish grey. Such a clot may be distinguished from a chicken-fat post-mortem clot in that it is friable and granular, is not elastic, and when removed by force it leaves a dull and roughened surface on the vessel wall.

The causes of thrombosis are (1) inflammation of the vessel walls, (2) injury to the wall, and (3) slowing of the blood stream. In surgical practice the first of these is illustrated by such conditions as lateral sinus thrombosis and puerperal sepsis, the second by thrombosis following the ligation of vessels, and the third by the form of thrombosis responsible for post-operative pulmonary embolism. Thrombosis is commonest in

veins. When associated with and dependent on inflammation of the vein wall the process is called *thrombophlebitis*, when not associated with inflammation it is best called *venous thrombosis*. It is venous thrombosis with the formation of the so-called bland thrombus which is responsible for post-operative pulmonary embolism, but the condition is of equal frequency in medical and surgical patients, the essential factor being the sudden confinement to bed of a previously active person. Martland has drawn attention to the importance of blunt force injury such as a fall or automobile accident; in many cases of fatal embolism the injury has been minor in degree.

Heparin inhibits thrombus formation by preventing the agglutination of platelets to form white thrombi. It has proved of great value in blood vessel surgery, permitting end-to-end anastomosis, suture of vessels, etc., without subsequent thrombosis.

Fig. 36.—Thrombus composed of laminae of platelets outlined by fibrin threads. × 100.

Dicumarol, like heparin, prolongs the coagulation time, and it has the advantage that the action is much more prolonged and that it can be taken by mouth instead of being injected intravenously as in the case of heparin. It has been used with success for preventing venous thrombosis in the legs and pulmonary embolism following abdominal and pelvic operations. It was discovered from the observation that cattle suffer from a hemorrhagic disease caused by eating decayed sweet clover. The hemorrhagic agent was isolated from the clover and finally synthesized. This agent is known as dicumarol.

The *sites* of thrombosis may be the veins, arteries or heart. Any inflamed *vein* is in danger of thrombosis; the veins of the leg are in danger in conditions of venous stasis. An *artery* becomes thrombosed if its wall is torn or injured, or if the smooth intimal lining is roughened by atheroma.

In the *heart* thrombus formation occurs in the auricles (particularly the auricular appendix) as the result of failing circulation, in the left ventricle over a recent infarct of the heart wall, and on inflamed valves where it gives rise to the vegetations which are the characteristic lesion of endocarditis.

Thrombophlebitis is often accompanied by some degree of edema of the part involved. The leg may be swollen from the foot to the thigh. Ligation of the femoral vein is not accompanied by edema, provided the lymphatics are left intact. It is probable that the edema is due to extension of the inflammation from the vein to the accompanying lymphatics. When the phlebitis subsides the swelling of the part clears up. An entity
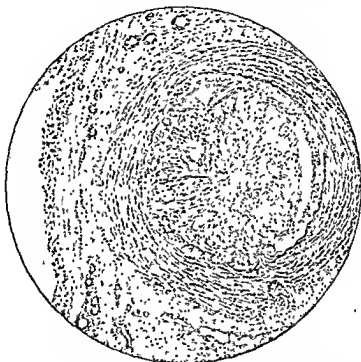
Fig 37.—Thrombus undergoing organization. The clot is becoming vascularized and invaded by fibroblasts.

quite distinct from and not necessarily associated with thrombophlebitis is *phlegmasia alba dolens*, the painful white leg which may complicate puerperal infection. The basis of the condition is a lymphangitis. The infecting organisms appear to have a special predilection for the lymphatics. The infection spreads from the uterus and cervix into the cellular tissues of the pelvis and down the lymphatics of the leg. The result is swelling, induration, and great pain due perhaps to involvement of nerve trunks. If the lymphatic block involves only the deep lymphatics the skin does not present the characteristic tense white appearance. One of the most serious features is that the swelling and induration of the leg are often permanent, a condition which may be regarded as a form of elephantiasis. For further details Goodall's paper should be consulted.

Subsequent Fate of the Thrombus.—After formation a thrombus contracts. It may then become absorbed or become organized.

Contraction occurs in every case, and is a phenomenon inseparable from the formation of fibrin. It is seen to best advantage when blood is collected in a wide test-tube; the clot shrinks away from the side of the tube, expressing in the process a large amount of serum. Similarly the clot in the vessel contracts. In doing so it may draw the vein wall with it, producing a puckering of the vein, or it may leave a space between the wall and the thrombus.

Absorption in part or in whole is of common occurrence. This is due to two main factors, softening and the activity of leucocytes. Softening of the center of the thrombus is probably due to lack of nourishment. Leucocytes play a most important part in the destruction of the thrombus, and are to be found in the clot in ever increasing numbers.

Organization of the thrombus occurs if absorption does not take place. From the spot in the vessel wall where the endothelium is injured there begins a peaceful invasion of vascular endothelium and fibroblasts. Solid buds of endothelium grow into the clot, these become canalized, and form an interlacing network of new capillaries. Fibroblasts grow in from the subendothelial connective tissue of the vessel, so that a vascular granulation tissue is formed (Fig. 37). Later this becomes dense and fibrous, and the vessels disappear.

If the thrombus shrinks away from the vessel wall, as usually occurs, the vascular endothelium will cover it so that the lumen will be re-established. Occasionally, but rarely, the blood may tunnel through the thrombus, which thus becomes canalized.

Lime salts may be deposited in an old thrombus with the formation of a *phlebolith.* These phleboliths are found in varicose veins in the leg, and in the pelvic and prostatic veins. In these positions they often form very striking objects in X-ray pictures.

EMBOLISM

An embolus is a body which, after moving for some distance in the blood stream, becomes impacted in an artery or it may be in one of the branches of the portal vein.

In the great majority of cases an embolus is a thrombus originating in the veins, the heart, or the arteries. Occasionally, however, other substances may play the part of an embolus. Of these the most important are tumor cells, clumps of bacteria, fat globules, and air bubbles. They will be considered subsequently.

The two commonest sites from which emboli start are (1) the veins of the leg, affected by venous thrombosis rather than thrombophlebitis because in the former the thrombus is less likely to be adherent, and (2) the heart. In the heart the thrombus may be formed in the right or left auricular appendix, or it may be in the form of vegetations attached to the aortic or mitral valves.

An aseptic thrombus is only friable and liable to become detached and start on a journey in its early stages. Later it becomes organized and firmly attached to the wall of the vessel by the ingrowth of new capillaries

and fibroblasts. It is in the early stages, therefore, that especial care must be exercised in handling the part.

A septic thrombus, on the other hand, is in a constant state of disintegration, and the danger of embolus formation is infinitely greater. The effects, moreover, of a septic embolus are proportionately more serious.

Results of Embolism.—The effect produced by an embolus will depend upon: (1) the nature of the embolus, whether septic or otherwise, (2) the extent of tissue affected, (3) the rapidity with which the obstruction is produced, and (4) the organ involved.

(1) *The Nature of the Embolus.*—When an aseptic embolus, such as may form in the auricular appendix, plugs a vessel the circulation is brought to a standstill, thrombosis occurs, and gradual organization of the thrombus ensures the completeness of the closure.

When, on the other hand, the embolus, derived from an inflamed vein or the vegetation of an acute endocarditis, is *septic* and contains masses of pyogenic bacteria, the sequence of events is very different Such a mycotic embolus may give rise to a suppurative thrombo-arteritis which, extending in turn through the vessel wall, sets up metastatic abscesses. One of the most beautiful illustrations of this process is to be seen in the kidney in the case of miliary abscesses following an acute streptococcal endocarditis. One part of the arterial wall may become weakened and give way, with the production of a small mycotic aneurism which may subsequently rupture, a not infrequent cause of cerebral hemorrhage in young people.

(2) *The Extent of Tissue Affected.*—This is self-obvious and requires no elaboration. Obstruction of a small branch of the pulmonary artery may pass unnoticed, whereas death may follow blocking of one of the main divisions. If the main artery to a limb is blocked gangrene may result.

(3) *The Rapidity with Which the Obstruction Is Produced.*—This is a factor of considerable importance. If the blood supply to a part be gradually cut off, the vessels can adapt themselves to the changed conditions in time to save the life of the part. Sudden obstruction, descending like a bolt from the blue, catches the part unawares and the tissues rapidly die. The time during which the obstruction is maintained is also of great importance, but this hardly applies to the case of embolism.

(4) *The Organ Involved.*—It has already been remarked that although embolism of the muscles of the limbs must be common, it seldom gives rise to symptoms sufficient to attract attention. In such an organ as the brain, on the other hand, even a minute lesion may be attended by dramatic results.

It is the type of blood supply of the part, however, which is the most important factor in determining the extent of the lesion. Given an abundant collateral anastomosis the effect of the embolism may be negligible. So rapidly is blood poured in from subsidiary channels that the engine never falters in its stride. The ordinary skeletal muscles afford an example of such a collateral circulation. Some organs, of which the best examples are the lung and the liver, possess a double blood supply. In such an organ obstruction of a small artery will produce no effect. It requires the blockage of a large vessel to make itself felt. Given,

however, a general circulatory disturbance of the part, such as chronic venous congestion of the lung, an embolus in a comparatively small vessel may cause trouble, because the collateral circulation cannot be efficiently established.

Infarction.—Other organs receive their blood supply through a single artery. Good examples of such an arrangement are provided by the kidney, the spleen, the branches of the internal carotid supplying the basal ganglia of the brain, and the central artery of the retina. When such an artery or one of its branches is blocked by an embolus, the corresponding area becomes acutely anemic and rapidly undergoes degenerative and necrotic changes. The process is called *infarction* and the affected area an *infarct*.

Necrosis is the chief feature of an infarct. The part dies en masse, but the general architecture is not interfered with, the outline of the cells can still be made out, and the connective tissue framework remains intact. The life has gone out of the part, however, and one is reminded, as Mac-Callum puts it, "of the appearance of charcoal as contrasted with that of living wood, or of the streets of Pompeii as contrasted with those of a modern town." The cells may maintain an orderly arrangement, but it is a city of the dead.

Infarcts are classed as *red* or hemorrhagic and *white* or anemic. In such organs as the kidney, spleen and lung they are characteristically wedge-shaped owing to the fan-like distribution of the vessels. Infarcts in the kidney and spleen are pale, but the surrounding vessels dilate in an attempt to set up a collateral circulation, so that the pale wedge is surrounded by a red border. In the lung infarcts are red, partly because of the double blood supply from pulmonary and bronchial arteries, partly because of extensive hemorrhage into the pulmonary alveoli. Even in such a type of infarct the alveolar walls undergo necrosis.

An infarct of the kidney or spleen becomes converted eventually into a mass of fibrous tissue, an infarct of the brain softens, liquefies, and gives rise to a brain cyst, but an infarct of the lung usually disappears entirely, so that an old healed pulmonary infarct is very seldom seen.

Pulmonary Embolism and Infarction.—The variety of embolism which is of more interest to the surgeon than all the others put together is that which involves the lung. There is no complication of an operation which is more dreaded. Robertson graphically describes the situation in these words:

"Fatal pulmonary embolism is a major tragedy, particularly when it afflicts patients following surgical operations, for almost all such patients are well on the road to recovery and without this catastrophe would probably be completely restored to a normal state of health. The operation is abdominal, and the more serene the events during and following the operation, the more likelihood there is of venous thrombosis and resulting embolism. Convalescence is peculiarly uneventful. Suddenly, almost out of a clear sky, there is a strange restlessness, rapidly ensuing shock with substernal distress, air hunger and collapse, and death usually in two to fifteen minutes. The horror of the patients' relatives is echoed by the poignant distress and shock of the attending surgeon, colleagues and nurses. After surviving the ordinary perils which may accompany any operation, and after assurance of cure is clearly manifest to all, like a stroke of lightning this unexpected agent of the grim reaper appears on the scene and wipes out at one blow the results of the otherwise successful operation and postoperative care."

The fatal embolus must be large in order to occlude one of the main branches of the pulmonary artery, and it usually starts as a bland thrombus in the femoral vein. Smaller emboli causing infarcts may originate in the lesser veins of the leg, the pelvic veins in women or the prostatic plexus in men. In such cases there is likely to have been a thrombophlebitis due to infection, whereas the largest emboli are due to venous thrombosis. A large bland thrombus is more readily dislodged than an infected one, as the former lies free, whereas the latter is attached to the inflamed vein wall.

The embolus may be many inches long and as seen in the pulmonary artery it has a characteristic coiled and twisted appearance (Fig. 38). There may be one large embolus or many small emboli scattered through the arterial tree in both lungs. The latter condition may be due to a larger embolus becoming fragmented, or to a series of emboli being discharged at intervals from the thrombosed vein. No thrombus may be found although the clinical history strongly suggested its presence. In such a case the thrombus may be represented entirely by the embolus in the pulmonary artery. The gun has been discharged, but not yet reloaded. Pulmonary emboli are frequently multiple, and it is common in fatal cases to find that the final episode has been preceded by minor attacks. It is in such cases that the prophylactic use of heparin holds considerable promise.

Fig 38 —Pulmonary embolus characteristically coiled.

The generally accepted view originating with Virchow and carried on by Aschoff and his school is that the thrombosis originates as a true platelet thrombus in the femoral vein and its valve-pockets; when the main vessel is obstructed, a red "coagulation thrombus" is supposed to form in the stagnant mass of blood in the peripheral vessels.

This theory has been called in question by a number of investigators whose work will be found summarized in Frykholm's paper. It now appears that there are four venous areas in which thrombosis may commence: (1) plantar veins, (2) the veins of the calf muscles, (3) the veins of the adductor muscles, and (4) the visceral pelvic veins. The frequency of incidence varies with the type of material examined. In gynecological and obstetrical patients the pelvic veins will head the list, whilst in young persons the plantar veins are most commonly involved. In Frykholm's material the principal sites were the calf and adductor regions (Fig. 39). It seems probable that a red or coagulation thrombus, in which all the elements of the blood are enclosed in a network of coagulated fibrin, is first formed in areas where the stream is sluggish, that the process extends in the direction of the blood flow, and that when a large vein

(femoral) is reached in which the stream is rapid platelets are deposited with the formation of a white thrombus. This is the part of the clot which is likely to be detached by some sudden physical exertion such as getting out of bed, coughing, or straining at stool. It is the youngest part of the clot not the oldest, and the process takes place in the reverse direction from that which has so long been believed.

It is generally conceded that three factors must be taken into consideration in the production of a thrombus: (1) slowing of the blood stream, (2) changed chemical composition of the blood, and (3) injury to the intima. Only the last-named can produce thrombosis without the

SECTION OF LOWER LEG

Vein distended

a

Vein collapsed

b
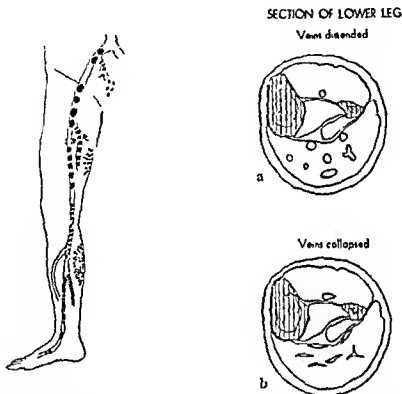
Fig. 39.—Principal sites of venous thrombosis in leg (Frykholm, Surgery, Gynecology and Obstetrics, 1940, 71, 306).

Fig. 40.—Effect of posture on veins of leg (Frykholm, Surgery, Gynecology and Obstetrics, 1940, 71, 306).

assistance of the others. Both stasis and changes in the composition of the blood occur as the result of operations, but they do not account for the sites at which the primary thrombus forms. Frykholm suggests that intimal injury is the essential factor. He points out that in a recumbent posture the veins of the leg collapse more or less completely (Fig. 40), and that this is especially so in the veins of the calf which are pressed on by the mattress and in those of the adductor region due to pressure of the thighs on each other, particularly in fat people. Under normal conditions the plantar veins are distended by the highest column of blood in the body, so that when the patient is confined to bed they are correspondingly collapsed. In a state of collapse the walls of the vein come together, and

intima is pressed against intima, more especially in those regions exposed to external pressure when the patient is in bed. As the nourishment of the endothelial cells depends in large measure on the blood with which they come in contact, there is reason to believe that these cells are injured by the continued pressure and may liberate thromboplastic substances which induce coagulation in the minimal stream of blood which percolates through the crack-like lumen. From this small beginning the process spreads upwards. As the collapsed veins become thrombosed, they are again distended to full size.

In support of this idea may be mentioned the fact that venous thrombosis has occurred in air-raid shelters in London, where elderly persons spend the night sitting in deck chairs which exert pressure on the back of the thighs and bring the walls of the veins together. In a number of cases this has been quickly followed by fatal pulmonary embolism. The importance of this conception (if true) is that it suggests new methods of prophylaxis. Instead of raising the foot of the bed to prevent stasis, the head of the bed is raised so that the veins are filled with blood and the walls prevented from coming together; this is done for one or two hours daily. Time will show whether this idea is sound.

Wharton and Pierson consider that almost 50 per cent of the deaths after gynecological operations are due to embolism and infarction. Cutler and Hunt, from an exhaustive consideration of the statistics from some of the best hospitals, conclude that one in every 30 to 50 patients operated on, no matter what the anesthetic, develops a pulmonary complication, and one patient in every 150 to 175 dies from some such complication.

The post-operative embolic phenomena may be divided into three groups.

(1) Cases of large emboli which occlude the pulmonary artery or one of its main branches, thus cutting off the blood supply to one or more lobes. A definite infarction does not result, but rather a widespread pulmonary edema without hemorrhagic consolidation. The result is fatal in 90 per cent of the cases. The patient is suddenly seized with acute respiratory distress, and may die in the course of a few minutes.

(2) Cases of emboli of moderate size, leading to hemorrhagic infarction and consolidation with pleuritic symptoms such as pain, and signs such as a friction rub. The mortality is from 15 to 20 per cent.

(3) Cases of very small emboli giving rise to mild but characteristic symptoms, but with few or no physical signs. Wharton and Pierson observed no deaths in their series of cases.

Pulmonary infarction usually occurs during the second or third week of convalescence. A useful generalization regarding the time of onset of complications after trauma is as follows: shock—three hours, fat embolism—three days, pulmonary embolism—three weeks. Fatal embolism, however, may occur during the first two or three days, I once saw three such cases in the course of a month. Infarction occurring at this early stage is fatal in about 50 per cent of the cases. There is one sign which may put the surgeon on his guard; the second week of convalescence should be afebrile, but cases which are going to develop infarction show a slight but persistent rise of evening temperature during that period.

It appears probable from the work of Henderson, Brown, and others

at the Mayo Clinic that a distinction should be drawn between the large embolus which results in the sudden death of the patient, fortunately an uncommon occurrence, and the more ordinary pulmonary infarct. The thrombus which accompanies phlebitis soon becomes attached to the wall of the vein, and under ordinary circumstances it is unlikely that a sufficiently large clot will become detached to block a main branch of the pulmonary artery. The thrombus formed in any cut vein will extend as far as the point of entrance of the next tributary vein. It is only when it extends further and projects into the blood stream of the large vessels that there is grave danger of it being detached and blocking one of the large pulmonary arteries. Henderson found that the patients who died of pulmonary embolism were older than the average surgical case, were overweight, and had a normal or subnormal blood pressure.

Best has prepared a moving picture film in color which demonstrates in the most dramatic way the relation of thrombosis to pulmonary embolism. He connected the carotid artery and jugular vein in an animal by means of a glass tube, the inner surface of which was scratched. Platelet thrombi can be seen forming as small white masses against the red background of the blood stream. As the observer is watching their formation they are suddenly whisked away and a moment later the animal manifests respiratory distress. Best and his associates found that the intravenous administration of heparin prevented thrombus formation not only in their glass chamber but also in veins whose walls were injured by either mechanical or chemical means.

The onset of infarction is characterized by a sudden sharp pleuritic pain in the side. There may be hemoptysis, but this is by no means a constant feature. The temperature does not rise to any marked degree until the second day (when fever may be quite pronounced), and physical signs of consolidation do not appear for two or three days. All these features serve to distinguish the condition from a true infective pneumonia. X-rays may show the presence of an infarct even though all the usual physical signs are lacking. The first noticeable change is a clouding of the costophrenic angle, the rest of the lung remaining clear (Wharton and Pierson).

The infarct presents the usual cone shape, the base of the cone producing *a slight elevation on the pleural surface.* The customary site is the lower lobe. On section it is solid, dark red in color, and of a friable texture. An old infarct may become grey.

Microscopically the alveolar spaces are filled with red cells and are quite airless. The alveolar walls are necrotic and disappear. Owing to collateral circulation from the bronchial arteries this infarct remains red and does not become decolorized. Absorption of the smaller infarcts usually takes place in the course of two or three weeks, and the circulation becomes reestablished. When the infarction is due to infected emboli there may be abscess formation or gangrene of the lung.

Embolism of the Superior Mesenteric Artery.—Although of infrequent occurrence, embolism of the mesenteric vessels is so dramatic in its manifestations that it demands separate consideration. The embolus, which usually arises in the left side of the heart from vegetations on the valves or a thrombus in the auricular appendage, produces infarction of

the bowel when it lodges in one of the larger branches of the superior mesenteric artery. Intestinal infarction may be caused by two factors other than embolism of the artery; these are thrombosis of the artery and thrombosis of the vein. *Arterial thrombosis* may usually be traced to atheromatous degeneration of the vessel wall. *Venous thrombosis* is often associated with one of two conditions, acute appendicitis or acute inflammation of the female pelvic organs; the infection may, of course, come in addition from many other sources. Arterial and venous mesenteric thrombosis are separate clinical entities. The arterial type is much more rapidly fatal. The venous type is probably more common, as the veins are likely to contain bacteria or toxins; the onset and course are slow, spontaneous recovery is possible as there may be hemorrhagic infarction without gangrene, and occult blood is always present in the stool. Venous thrombosis may be primary or secondary. Primary thrombosis due to an endophlebitis or phlebosclerosis is a rare condition. Venous thrombosis is nearly always secondary either to injury to the vessel wall (constriction from strangulation, etc.) or to inflammation of the bowel wall (most frequently acute appendicitis). In the terminal stages it is difficult to determine if the inflammation of the organ is the primary condition or if the venous thrombosis has been responsible for the death of the bowel wall. A patient may die after an operation for simple acute appendicitis, and at autopsy the mesenteric thrombosis responsible for the catastrophe may be hidden by an extensive peritonitis.

It may appear strange that a part in which the collateral circulation is so abundant should be subject to infarction. How is it that a circulation, which from the anatomical point of view is so rich in anastomoses, yet behaves as if it were a terminal one? It is because the sudden anemia produced by blockage of one branch of the artery sets up so violent a spasmodic contraction of the musculature of the bowel that the part becomes isolated from the neighboring circulation. Moreover this spasm aggravates the anemia to such a degree that death of the affected segment of the bowel speedily results.

The infarction, which is always of the red or hemorrhagic variety, usually affects the lower part of the jejunum and the ileum. There have been occasional cases in which embolism or thrombosis of the main artery has resulted in hemorrhagic infarction extending from the lower part of the duodenum to the transverse colon.

The affected portion of bowel is thickened, dark red in color, and soon becomes gangrenous. The limits are usually sharply defined, but the demarcation may be more gradual. The entire bowel wall is stuffed with blood, the mucosa is necrotic and may be ulcerated, the lumen contains thick tarry blood, the serous coat is covered by an inflammatory exudate, the peritoneal cavity contains bloody fluid, or there may be a general peritonitis. The mesentery is thickened and contains large patches of hemorrhage; the mesenteric veins are greatly engorged, and the mesenteric glands are swollen and hemorrhagic.

In some cases the degree of infarction is much less complete, and the hemorrhage may be confined to the mucosa. Occasionally the signs of infarction may be present although no obstruction can be found in the mesenteric vessels. In an autopsy on one such case I found a remarkable

condition of large hemorrhagic patches through the lower part of the small intestine, although no lesion could be detected in the vessels.

Obstruction of the inferior mesenteric artery is much less frequent than that of the superior mesenteric, nor is it so serious in its results, for the artery is not a terminal one, communications being established with the middle and inferior hemorrhoidal arteries below, and with the superior mesenteric above. In spite of this, however, obstruction is frequently followed by the production of a hemorrhagic infarct, but gangrene is not likely to develop.

The clinical picture is that of acute intestinal obstruction, the symptoms developing with great rapidity. The first symptom is sudden acute abdominal pain, due to spasm of the bowel from the sudden anemia. The pain, although constant, is marked by acute exacerbations, perhaps owing to the intestinal contractions. One of the most significant and suggestive symptoms is the passage of blood by the bowel, which may lead to a mistaken diagnosis of intussusception. Blood may also be present in the vomited material. At first there may be diarrhea, but this is followed later by complete obstruction.

Fat Embolism.—Fat globules may enter the circulation and form emboli. This occurrence is probably quite frequent as the result of fractures, operations on fat subjects, and crushing injuries, but it seldom gives rise to serious results. At the same time, as Warthin points out, the possibility must be borne in mind in all injuries to bone. The fatal cases have been wrongly diagnosed as shock, coma, concussion, etc. The veins are torn much more readily than the arteries, so that the fat enters

Fig. 41.—Fat emboli (stained black) in brain. × 160.

the venous circulation and is carried to the lungs; where it may be arrested in the alveolar walls. It will not be detected in paraffin sections, being dissolved out in the process of preparation, but can readily be demonstrated in frozen sections stained for fat. Robb-Smith suggests a method by which the fat can rapidly be demonstrated in the autopsy room. A thin snippet of lung is placed on a slide and a few drops of 2 per cent potassium hydroxide are added. This clears the tissue, and the fat droplets can then be seen with the low power of the microscope when the diaphragm is closed. Emboli are more likely to be detected by this method than in a thin microscopic section. If the emboli in the lungs are very numerous they may cause pulmonary edema and symptoms of surgical shock; fat globules may be present in the sputum. The emboli may pass through the pulmonary capillaries and lodge in the brain or kidney (Fig. 41). In the brain they will lead to petechial hemorrhages in the white matter, whilst their presence in the kidney may be indicated by

the presence of droplets of fat in the urine. There may be two quite distinct types of clinical picture as the result of fat embolism: these are the pulmonary and the cerebral. The *pulmonary type* manifests itself in the first two days after injury, and is marked by a violent dyspnea with cyanosis and pulmonary edema due to widespread obstruction of the capillaries and arterioles of the lungs by fat emboli. The *cerebral type* is marked by symptoms of cerebral irritation followed by stupor deepening into coma. Death may occur from two to seven days after receipt of the injury. Harris points out that there may be a profound fall in hemoglobin due to the loss from circulation of great numbers of erythrocytes poured into the pulmonary alveoli. This will not be present in rapidly fatal cases nor in mild cases. The diagnosis is easily missed both by the clinician and the pathologist. The sequence of events is always suggestive: an injury to bone, a clear interval, the development of pulmonary symptoms and later cerebral symptoms. The presence of fat globules in the sputum and urine together with a great fall in hemoglobin are confirmatory features of real value.

The obvious explanation of fat embolism is the entry of fat into the circulation. The objection has been raised, however, that the quantity of fat found in the capillaries throughout the body is too great for this simple explanation, and it has been suggested that the basis for the condition may be a change in the physico-chemical state of the normal blood fats with loss of emulsification as the result of trauma. It is postulated that the traumatized tissue may liberate a lipo-proteinase which brings about this change. Such an explanation seems more far-fetched than the original one. It is remarkable how much fat may be expressed from traumatized marrow, and when this becomes minutely subdivided it may give rise to incredible numbers of droplets capable of blocking capillaries.

Air Embolism.—Air may enter the circulation if one of the large veins in the neck is opened during an operation, or as the result of artificial pneumothorax. It occurs about once in every 500 to 1000 pneumothorax treatments. In the vast majority of cases no harm results. The rare fatal cases may be due to the air converting the blood in the heart into a froth which makes proper cardiac contraction impossible, or bubbles of air may reach the brain. When a vein in the neck is cut in the course of an operation on the thyroid, the first sign is a hissing sound in the wound, the so-called "sifflement," as air is sucked in. The result may be dyspnea, cyanosis, coma, and finally death. Many cases are due to the injection of air, with or without fluid, into the uterus in the production of criminal abortion; the placenta becomes separated, and air enters the large uterine veins. My colleague Dr. W. L. Robinson encountered five such cases in a comparatively short period. In these latter cases the inferior vena cava is distended with bubbles of air, and should be inspected before the heart is removed.

Primary Thrombosis of Axillary Vein.—This rare but readily recognized condition is characterized by a history of recent trauma or exceptional effort, swelling of the affected arm from the fingers to the base of the axilla, slight cyanosis of the skin, dilatation of the superficial veins over the anterior and lateral aspects of the chest wall, and the presence of a firm tender cord which can be felt along the line of the axillary vein.

The prognosis is uniformly good without removal of the thrombus. The striking feature is the suddenness of the attack and the rapidity with which the swelling spreads over the arm. No completely satisfying explanation has been suggested for the condition. The patient is usually young, robust, and engaged in heavy labor. He may have been exposed to habitual occupational strain. Matas quotes the following instances: a waiter who became fatigued after waiting several hours at table, a woman who was stricken after beating wash clothes with a heavy stick, a girl of nineteen who had given the Christmas pudding prolonged and vigorous stirring. In other cases a single violent effort has been followed by the onset of thrombosis. Very rarely the onset appears to be spontaneous with no history of injury or strain. It seems probable that the chief local etiological factor is overstretching and contusion of the axillary vein between the clavicle and the first rib, the costo-coracoid ligament and the subclavius muscle. The latter muscle by sudden contraction may rupture the delicate subclavio-axillary valve which underlies this muscle, thus creating an endophlebitis and thrombosis.

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CHAPTER VII

SURGICAL SHOCK

The subject of shock is one which has exercised the medical profession for many years, more especially since the development of abdominal surgery. This mysterious and sinister condition is liable to develop after: (1) extensive operations, particularly those involving handling of the abdominal viscera; (2) acute abdominal catastrophes (perforation of stomach or bowel, strangulated hernia, acute pancreatitis); (3) severe injuries; (4) extensive hemorrhage.

The patient in a condition of profound shock presents a very *characteristic appearance*. He lies perfectly still, and pays no attention to what is going on around him. The face is overspread by an ashen-grey pallor, large drops of sweat hang from the eyebrows, the eyes are weary, lusterless, and deeply sunken in their sockets, the cheeks hollow, the brow furrowed with anxiety, the skin cold and clammy. Four of the vital processes are notably depressed: (1) the temperature is subnormal; (2) the pulse is extremely feeble, running, and irregular; (3) the respirations are shallow and sighing; and, most important of all, (4) the blood pressure falls very low. Although plunged in mental torpor the patient is quite conscious and answers questions slowly, painfully, but correctly. Shock, fortunately, is a temporary condition; it is a step toward death, but a step which the patient can retrace in a few hours.

Causes.—Moon puts the matter in a nutshell when he remarks that the shock syndrome results from a disparity between the volume of blood and the volume-capacity of the vascular system. There may be a decrease in the blood volume, an increase in the volume-capacity of the vascular system, or a combination of these. The blood volume may be decreased by hemorrhage, and by transudation of serum through the capillary walls with resulting increased concentration and viscosity of the blood and rise in the red cell count and hemoglobin percentage (an important factor in shock due to severe burns).

The principal aim of treatment is to replace the blood volume. This can be done by blood transfusion, but it is the plasma rather than the red blood cells which is of value; if the volume can be maintained, the corpuscles are quickly replaced. Now that blood serum can be desicated and stored indefinitely in dried form, only requiring the addition of distilled water, the difficulty of getting blood donors of the appropriate group has been overcome. This is of inestimable value in military surgery.

A distinction must be drawn between *traumatic shock* which follows immediately on the receipt of a severe injury and *secondary shock* which may not develop for twenty-four hours. In traumatic shock the chief factor is the discharge of nociceptive nervous stimuli which lead to *widespread capillary paralysis*. In secondary shock the commonly accepted explanation of the capillary paralysis is the widespread action of

a histamine-like substance liberated as a result of the bruising of muscles. During the first world war Bayliss and Cannon showed that experimental bruising of muscles in animals was followed by shock, but if the main vessels of the limb were first tied no shock developed. Injection of extract of the bruised muscles produced the same effect. Dale has shown that the *injection of histamine*, a cleavage product of protein, produces an identical result. The observations of Blalock have thrown doubt on this explanation of secondary shock. Blalock points out that bruising of muscles is accompanied both by hemorrhage into the part and by a great extravasation of serum due to increased permeability of the capillaries. There is therefore a great decrease in the volume of the blood with resulting shock. *Accessory factors* undoubtedly play a part. Thus cold, exhaustion, depression, and general anesthesia (especially ether and chloroform) predispose to the development of shock. It has been said, with what truth it is difficult to determine, that shock is more common after a lost battle than after a victory.

It has been shown experimentally by Moon that exposure of the abdomen to high voltage radiation causes physiological disturbances identical with those of shock from other causes. There is the same hemoconcentration and the usual lesions. The exposure to radiation causes delayed necrosis of the intestinal mucosa. Absorption of cytoplasmic material from this damaged tissue seems to produce the physiological disturbances.

Nature of Shock.—Shock, like eclampsia, might be called "the disease of theories," and several pages might be filled in discussing them. It is probably a mistake to look for a single causal factor; in most cases of shock in man a variety of factors come into play. Moon's definition of shock as "a circulatory deficiency, not cardiac or vasomotor in origin, characterized by a decreased volume of blood and cardiac output and by hemoconcentration" suggests the possibility of a multiplicity of factors. The essence of the condition seems to be a relative disappearance of blood from the heart and great vessels, so that the heart has not sufficient fluid on which to contract. This blood was supposed to disappear into the splanchnic veins, but it now appears certain that the capillaries form the real reservoir, and the patient bleeds into his own capillaries (or into his tissues—Blalock). In a state of health only a small amount of the capillary bed is open at any one time. The blood flows through only a limited number of glomeruli in the kidney at the same time. According to Krogh the volume of blood in the active muscles of a guinea pig may be 275 times as great as when the muscles are at rest, and if the entire capillary bed were opened up there would be 750 times as much blood. If, then, something can paralyze the vast capillary bed of the body and cause it to dilate, the blood will disappear into it as if sucked up by a sponge, the blood-pressure will fall, the heart will be unable to beat properly, and the brain will suffer from anemia.

The *lesions* are those which might be expected from these general considerations, as Moon and Kennedy have shown both in the experimental animal and in man. They are most marked in the lungs and the gastro-intestinal tract. The lungs are dark and filled with blood. Microscopically the capillaries are widely dilated and the alveoli are filled with

fluid; it is a picture of pulmonary congestion and edema. In the wall of the intestine the increased capillary permeability is evidenced by petechial hemorrhages and edema. The picture is thus the reverse of that seen in severe hemorrhage. Many of the signs and symptoms of shock and hemorrhage are identical, and hemorrhage may be an important factor in the production of shock, but the two conditions are entirely distinct.

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CHAPTER VIII

TUMORS

A tumor is a growth of new cells which proliferate without control, and which serve no useful function. It is therefore called a new growth or neoplasm. Many new formations occur in the body which are not true tumors: the callus following a fracture of bone, the physiological hypertrophy of the breast and uterus, the granulomatous masses characteristic of syphilis and tuberculosis. It is probable that some conditions at present regarded as tumors may later be recognized to be due to some other cause.

ETIOLOGY

In discussions on etiology of tumors two mistakes are commonly made: (1) that there must be one and only one single definite "cause of cancer"; (2) that no progress has been made as the result of the investigations of those engaged in cancer research. There is no reason to believe that all tumors are caused by the same agent, any more than there is reason to believe that all infectious fevers are due to the same cause. It is true that theory after theory has come up as a flower, only to be cut down like the grass, and that the veil of mystery has not yet been rent in twain, but it is even more true that during recent years enormous strides have been made in our understanding of the general process of neoplasia.

Recent advances in cancer research are concerned chiefly with chemical carcinogenic compounds, sex hormones, and filtrable viruses.

Chemical Carcinogenic Compounds.—In 1775 Sir Percival Pott observed that cancer of the skin was especially common in men who worked with tar, and he offered the suggestion that the tar acted in some manner as a causal agent. In 1915, that is to say 140 years later, Yamagiwa in Japan put this idea to the test by painting tar on a rabbit's ear every day for over six months. At the end of that time carcinoma developed at the site of tarring. For the first time in cancer research it was possible to produce a malignant tumor at will quite independently of any preexisting tumor. This was an epoch-making discovery, and served as the starting point of a series of investigations of the greatest importance.

Tar is a highly complex substance containing a great variety of chemical agents. The next step was to determine the active agent or agents present in tar which were responsible for producing the cancer. This step was taken by Kennaway and Cook in 1932, when they succeeded in isolating the hydrocarbon benzpyrene from tar and showed that it possessed a high degree of carcinogenic activity. It was then noticed that benzpyrene gave a spectum with flourescent light very similar to that of a group of recently synthetized hydrocarbons, of which one of the important members is 1:2:5:6 dibenzanthracene. On following up this lead it was at once found that the latter substance was powerfully carcinogenic, and as it had the advantage of being a chemically pure substance of

known composition, it has become the most popular agent in the experimental production of cancer. It is interesting to note that 1:2 benzanthracene has practically no carcinogenic activity, but the attachment of a new benzene ring in the 5:6 position gives it great carcinogenic power.

Another of the chemical carcinogenic compounds is the cholanthrene group. Cholic acid, an organic substance occurring *naturally* in the body, can be converted by chemical means into methylcholanthrene, a hydrocarbon related in structure to the synthetic hydrocarbons which have just been described. On trial it was found that cholanthrene and methylcholanthrene were amongst the most powerful carcinogenic agents known. It is the presence of the five-membered ring, known as the pentacyclic system, not the methyl group, which confers on the compound its carcinogenic power. When this substance is painted on the skin it produces carcinoma, when injected subcutaneously it produces sarcoma. It will be observed that both methylcholanthrene and benzpyrene, the original carcinogenic substance isolated from tar, contain the 1·2 benzanthracene ring system, although that system itself is almost completely lacking in activity.

To summarize this brief review of the chemical carcinogenic compounds, three main groups may be recognized. (1) Benzpyrene, the original carcinogenic hydrocarbon isolated from tar. (2) The benzanthracene group; 1:2 benzanthracene is practically inert, but 1:2.5:6 dibenzanthracene is extremely potent. (3) The cholanthrene group, which is benzanthracene with the addition of a five-membered ring.

Any of these agents can produce either carcinoma or sarcoma at the site of application. If applied to an epithelial surface carcinoma develops, if injected subcutaneously sarcoma is the result. By this means it has been possible to produce carcinoma of the skin, kidney, liver, testis, bladder, and uterus, as well as sarcoma of the sucutaneous tissue and peritoneum. In at least one instance the effect is produced at a distance; 1·2·5·6 dibenzanthracene has no effect when introduced into the air passages, but when painted on the skin or injected subcutaneously in mice of a lung-cancer strain, it hastens the development and increases the incidence of lung tumors.

It must not be supposed that the only potent carcinogenic agents are the hydrocarbons. Clinical observation has long shown that arsenic has carcinogenic power when taken as a medicine for too long a period. So simple a substance as zinc chloride can induce the growth of so complicated a tumor as a teratoma when injected into the testicle of a rooster. The Spirochaeta pallida is well known to act as a carcinogenic agent when located in the tongue.

While the work on the carcinogenic hydrocarbons was going on, organic chemists were investigating bile acids, the sterols such as chlosterol, and the sex hormones, and soon it became evident that the basic structure of these very different substances was fundamentally similar (Fig. 42). All of them possess the condensed-carbon-ring skeleton known as the phenanthrene nucleus, and this nucleus is also present in the benzpyrene, benzanthracene and cholanthrene groups of carcinogenic hydrocarbons. At first it seemed as if the phenanthrene nucleus might be the key to carcinogenesis, but later, as has always happened with the cancer problem.

this delightfully simple idea had to be abandoned. We have already seen that methylcholanthrene, which from its structure is seen to belong to the sterols, can be produced from bile acid by a series of processes which might well occur in the body. It becomes evident, then, that there is a structural relationship between the chemical carcinogenic compounds and the normal constituents of the body, and we must admit that it is theoretically possible for carcinogenic agents to be produced within the body as the result of disordered metabolism affecting the sterols, bile acids or sex hormones.

Sex Hormones.—From the structural resemblances between the carcinogenic hydrocarbons and the female sex hormones it might be deduced that their physiological activities are also similar. Such indeed proves to be the case. Certain of the hydrocarbons, such as benzpyrene, are able to replace the female sex hormone, whilst the administration of estrin may

PHENANTHRENE DIBENZANTHRACENE ESTRONE
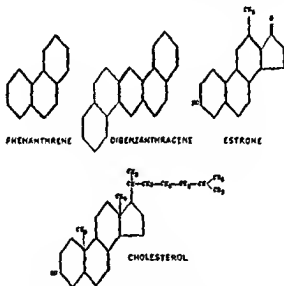
CHOLESTEROL

Fig. 42.—Similar chemical structure of carcinogenic hydrocarbons, estrone, and cholesterol.

result in cancer. Thus carcinogenic substances can be estrogenic, and estrogenic substances can be carcinogenic. Estrin does not act locally on the skin or subcutaneous tissue like the carcinogenic hydrocarbons; it acts on the mammary epithelium which is normally under the influence of ovarian stimulation. Lascassagne has shown that if estrin is injected from birth onwards into a strain of mice which have a natural tendency to develop mammary cancer, the incidence of that tumor is very greatly increased, and even in male mice of the same strain mammary cancer can be produced, although the natural occurrence of this tumor in the male is almost unknown. Even when the hormone is painted on the skin it produces its characteristic effect on the breast. It is important to note that if mice of a non-cancerous strain are used, the hormone is powerless to produce cancer. Removal of the ovaries at an early age in mice of a high cancer strain will prevent the occurrence of spontaneous mammary cancer, but administration of estrin will cause cancer to develop. Carci-

noma of the cervix has also been produced by the prolonged administration of estrin.

Filtrable Viruses.—In 1910 a discovery was made which excited surprise and incredulity at the time, but the full significance of which has only been realized in recent years. In order to transfer a tumor from one animal to another, living tumor cells must be implanted into the second animal. This was universally recognized. But in 1910 Peyton Rous made the revolutionary observation that if an emulsion of a certain fowl sarcoma was passed through a filter, the fluid which passed through was carcinogenic, although the cells were held back by the filter, that is to say it contained some agent which had the power of initiating an entirely new tumor in the second animal, not merely a continuation of the tumor of the first animal. During the intervening thirty years Rous has always referred to the filter-passing principle as "the agent," but it is now generally agreed that the active agent of this and of many similar tumors in birds which have since then been discovered, is a filtrable virus. These tumors are known as the filtrable tumors. One such tumor, an adenocarcinoma of the kidney, has been described in the frog.

The surgeon is naturally interested in the possible relationship of the filtrable tumors of birds to human cancer. Only one filtrable tumor has been discovered in a mammal, a benign cutaneous papilloma of wild rabbits shown by Shope in 1933 to be due to a filter-passing agent, presumably a virus. When this tumor is transferred to the domestic rabbit the papilloma grows more rapidly and frequently develops into a carcinoma. It is of particular interest to note that when this occurs, the virus can no longer be separated from the tumor, so that the tumor is no longer filtrable. It would appear that the virus has become so firmly united with the malignant cell that dissociation is no longer possible. This suggests a possible explanation why it has not been possible to obtain filtrable agents from mammalian cancer. Or again, there may be a filtrable agent, but it may be more unstable than that of avian tumors.

When the virus of the Rous sarcoma is injected into a bird a malignant tumor develops at the site of the inoculation. It might be supposed therefore that the virus remains localized to this site. Mellanby has shown that this is not the case. The Rous agent is widely diffused throughout the body, being found in the spleen, liver, muscle, brain and other organs, as can be shown by the injection of cells or cell-free filtrates of these organs into other fowls. And yet tumors of these organs do not develop.

The carcinogenic activity of hydrocarbons and viruses may be combined, as has been proved by the later work of Rous. We have already seen that the production of cancer of the skin in a rabbit by tarring is a very slow process. If after a month or two of tarring the Shope papilloma virus is injected intravenously, a rapidly growing carcinoma will quickly develop in the tarred area. It may be that the tar reaction serves to anchor the virus to the cells. Other examples might be given. Thus the presence of linen threads in the subcutaneous tissue greatly accelerates the production of a sarcoma by 1:2:5:6 dibenzanthracene, whilst estrin hastens the action of heredity in relation to cancer of the breast. It is evident that different carcinogenic forces may act in unison.

A particularly interesting observation on the association of chemical

carcinogenic agent and virus was made by Parsons in 1936, who produced 1:2:5:6 dibenzanthracene sarcomas in mice, and found that in 2.5 per cent of the tumors (grafted through several generations), a cell-free filtrate would reproduce the tumor when injected. In other words, a virus appeared to have developed at the site of action of the carcinogenic chemical.

Heredity plays a very important part in experimental cancer work in the laboratory. It has been shown by Maud Slye and many subsequent workers that it is possible to breed a strain of mice which is practically 100 per cent liable to develop cancer of a particular organ (lung, stomach, etc.), and another strain which is practically immune. It has been truly said that pure strains of animals of known hereditary tendencies are as important for cancer research as pure chemicals are for the chemist. What is inherited appears to be a poorly balanced cell system, in which the equilibrium is easily upset and malignancy develops. This upset may be due to excessive functional strain or to some unfavorable environmental condition. Every cell may be considered as potentially malignant, but the degree of potentiality varies greatly. If the tendency is sufficiently great the strain of normal physiological function may be enough to start the process. If less marked, functional overstrain may be sufficient. If the potentiality is only slight, some external carcinogenic agent may be needed to break down the resistance. Thus the ease with which a tumor may be induced experimentally depends on the genetic make-up of the host. As an example of undue functional strain we may take a race of mice with a high incidence of mammary carcinoma. This incidence can be raised considerably by forced breeding, it can be markedly reduced by preventing breeding, and it can be abolished by castration before puberty. Males of this strain if castrated and engrafted with ovaries or injected with estrin will develop mammary carcinoma in the same incidence as the virgin females. Ligation of the milk ducts will also increase the incidence. On the other hand if the strain is not a cancerous one, no mammary cancer will be produced either by estrogenic hormones or by duct blockage. In the experimental animal the hereditary weakness affects one organ or tissue rather than the whole body. Thus a mouse with marked tendency to develop cancer of the lung may be more resistant to the effect of a chemical carcinogenic agent on the skin than a member of n low lung-cancer-rate strain.

To apply these results to human material is a task of great difficulty for obvious reasons, but the feeling is growing that the genetic factor is of real importance in cancer in man. The occurrence of "cancer families" has long been described in the literature. If both parents are cancerous one might expect to find a marked cancer incidence in the children, although many of these may die of other diseases before they reach the cancer age. In one family cited by Warthin, a cancerous mother and a cancerous father had six children; all died of cancer as did the only grandchild. Thus the entire family of nine members in three generations died of cancer. The susceptibility may apply to one particular organ. Thus Warthin observed a family where four brothers died of cancer of the lip. The same type of cerebral tumor may develop in the same part of the brain in identical twins at the same age.

Having reviewed the factors which may be responsible for carcinogenesis in the experimental animal, we may consider briefly the cancer process as a whole. Malignancy is essentially a property of automatic division, a fundamental change in cell physiology, which develops suddenly, is transmitted to descendants, and bears no relation to the agent which starts it. The process may be regarded as a perverse physiological phenomenon, involving the internal control mechanism of the cell. In these respects it is therefore entirely different from an infective process.

A common characteristic of carcinogenic agents of whatever type (with the exception of the viruses) is the long period of time required to produce cancer. The same is probably true of cancer in man. It would appear that the process of carcinogenesis consists of two phases: (1) a process of long duration which induces a condition of potential malignancy, corresponding to precancerous conditions in man; (2) sudden change of potentially malignant into malignant cells. In any case we must not confuse carcinogenesis with the cancer process itself. The two processes, starting and continuing, are quite different. A match, an electric spark, or chemical combustion may start a fire, but the spread of the fire is due to the liberation of potential energy hitherto locked up in the combustible material, and bears no relation to the initial cause.

When cancer is considered from the standpoint of the extrinsic cause, it can be regarded as many diseases rather than as a single entity. But in respect to the intrinsic or proximate cause (what happens in the cell when it changes from the normal to the malignant state), all malignant cells have the same biological properties, *i. e.*, the intracellular change seems to be the same in all malignant cells; in this sense cancer is a single disease. Cancer can be produced in a bewildering variety of ways. At the same time it must be borne in mind that "the mere fact that one can imitate a natural process by the use of an artificial agent does not prove that one has discovered the actual agent by which the natural process is brought about ... the line of investigation that now requires to be followed in cancer research is not so much the production of tumors by artificial means as, what is incomparably more difficult, the discovery of the actual factors by which the naturally occurring tumors are induced." (Cook.)

Irritation.—Clinical evidence points very strongly to the close relationship between chronic irritation and some forms of malignant disease. Indeed, it may almost be said that cancer does not develop in a normal tissue. Some of the more important examples are the following: cancer of the lip and heavy smoking, cancer of the tongue or cheek and a jagged denture or syphilitic glossitis, cancer of the cervix uteri and lacerations resulting from childbirth. Roentgen-ray-workers, chimney-sweeps, paraffin-workers, and workers with aniline dyes are apt to develop cancer of the skin in the part exposed to irritation. Bones which have become highly radio-active owing to the person swallowing radio-active substances (workers with luminous paint) are apt to be the seat of sarcomatous growth. Ross inserted radium-filled platinum needles in the tissues of 9 rabbits; 6 of these developed malignant growths in immediate relation to the needles. One of the most striking examples is cancer of the abdominal wall (kangri cancer) in the natives of Kashmir who carry a

hot basket of charcoal, the kangri, under their clothes for purposes of warmth; it is striking because cancer in this region is almost unknown in other races. Cancer may develop in the scars of old burns which are apt to break down (Fig. 43).

With regard to the relation of chronic irritation to cancer it may be pointed out that such carcinogenic agents as tar and oil are soothing substances, whereas irritants such as acids and alkalis never cause cancer. Moreover, some compounds which are irritating do not produce cancer, while their isomers, some of which are non-irritating, are carcinogenic. A very slight change in the chemical structure of a substance may convert it from a non-carcinogenic into a carcinogenic agent. Thus the irritation which results in cancer must be regarded as a special kind of irritation.

Trauma.—The relation of a single trauma to the development of cancer is very important from the point of view of compensation, but presents an almost insoluble problem. When a tumor appears the patient often recalls having received a blow on that part not long before. The breast is a common example. This, of course, is no proof. It is safe to say that there is not a single case in medical literature in which it can be conclusively proved that trauma was the cause of the tumor, because it is not possible to be certain that the tumor was not there before. Only the experimental production of a tumor by a single trauma would be proof. Ewing points out that mammary cancer in mice can be produced at will by overstimulation with estrin, and cancer of the skin by dibenzanthracene, but that no one has ever produced cancer in the mouse by trauma. Trauma frequently reveals and aggravates a tumor, but that is very different from causing it. "Whenever an apparently trivial injury

Fig. 43.—*Epidermoid carcinoma of leg following upon a chronic ulcer.*

is said to have produced some peculiar and exaggerated effect, and a tumor is later discovered, it should raise the suspicion that the tumor antedated the injury. The probability of coincidence is much greater than is generally recognized." (Ewing.) The most likely cases where there may be some relationship are osteosarcoma and glioma of the brain, but even here there can be no certainty. A trauma may be responsible for a secondary tumor just as it may cause osteomyelitis. Hemorrhage occurs at the site of injury and the tumor cells circulating in the blood are arrested.

It is impossible to state with any assurance the relative importance of the intrinsic factor such as heredity and the extrinsic factors such as irritation or trauma. There are some persons and animals in whom no extrinsic factor will cause cancer; there are probably others in whom several such factors may precipitate the condition. If the extrinsic factor acts with sufficient intensity and duration it may act almost alone, and the reverse is also true. Champlin records the case of two brothers who were identical twins. One died of sarcoma of the right testicle at the age of thirty-one years. The other was struck on the right testicle with a board and shortly afterward developed sarcoma of that testicle, from which he died at the age of twenty-six years. Had he escaped the injury he would have developed sarcoma of the testicle at the age of thirty-one years. Here we have a striking example of both the intrinsic and extrinsic factors at work. In the family described by Warthin and mentioned on a previous page, three brothers were heavy smokers and died of cancer of the lip between the ages of forty and forty-five years. The fourth was a nonsmoker and died of cancer at the age of sixty-three years, so that the absence of the extrinsic factor may have increased the span of life by twenty years. The intrinsic factor may be so overwhelmingly strong that no extrinsic factor is necessary, as in the family described by Leschziner where a mother and three daughters died of cancer of the breast at the ages of twenty-two, twenty-one, nineteen and fourteen years.

Biopsy Examination.—A biopsy is the examination of a piece of tissue removed during life. In his Beaumont Foundation Lectures Ewing says that "the resort to a biopsy is a confession of failure, due to clinical inexperience or lack of data from other methods of diagnosis." The effect of radiation may give more reliable diagnostic information than the biopsy. Thus in tumors derived from radio-sensitive cells, embryonal carcinoma, teratoma of the testicle, Ewing's tumor of bone, and chondrosarcoma, the radiologist is often more likely to be right than the pathologist.

In spite of these facts it remains true that a biopsy is a procedure of the greatest value. The fate of the patient may depend on a correct report, and it is the duty of the surgeon to take certain precautions in removing the specimen. In the case of a doubtful breast tumor two procedures are available, incision or excision; each has its supporters. The lump may be excised and handed to the pathologist in the operating room for quick section. Or it may be incised, the cut surface inspected, and a piece removed for section. In the opinion of many surgeons this is less likely to open up lymph channels than the passage of the knife through the outer zone of a carcinoma. A small ulcer of the lip should be excised in its entirety and then examined. The surgeon will not wish to remove a large ulcerated area on the tongue, cervix or rectum if it should prove to be innocent. Here it is sufficient to excise a piece of the edge of the ulcer. If the lesion on the tongue or cervix is malignant it is an epithelioma which is recognized by infiltration of the deeper parts. The section must therefore go deep. A shaving of the surface is worse than useless. In the rectum a malignant tumor will be an adenocarcinoma, so that a more superficial section will suffice. The tissue must be placed at once in a fixative (10 per cent formalin, etc.). This is of particular importance when

the specimen has to be sent in from a distance. The worst thing that can happen to a small piece of tissue is to be allowed to dry.

Tumors of lymph nodes and bone are particularly hard to diagnose by physical examination, so that the clinician turns to the pathologist for assistance. Removal of an isolated lymph node is a harmless procedure, and sometimes gives valuable information. But removal of a lymph node in diseases of the lymphatic system is much overdone. If the physician, after a careful clinical and blood examination, is still in doubt, the pathologist is also likely to be in difficulty. The therapeutic test by radiation is much more likely to throw light on the case; inflammatory lesions will be made worse; the malignant lymphomas respond with varying degrees of readiness. Biopsy on bone tumors, on the other hand, should only be undertaken with reluctance. The shell of bone around the tumor serves as a barrier to invasion of the soft parts, and when this is broken down by the knife sarcoma cells may pour through the gap and give rise to a fungating tumor which bursts through the skin. Moreover radiological examination will often give as reliable evidence of the nature of the lesion as microscopic examination. There is, of course, a place for the biopsy in the diagnosis of bone lesions, but the method is often used without discrimination. As regards microscopic diagnosis in general, one of the most difficult tasks is to differentiate between sarcoma and inflammatory tissue.

When the surgeon considers that a lesion is malignant and the pathologist's biopsy report is that it is benign, the surgeon should never accept that report without question. There should be a consultation between the surgeon and the pathologist, as a result of which the latter may change his opinion. If he has not the courage to do so he is not fit to be a pathologist. Should they fail to agree, then the pathologist should see the patient, as a result of which he may find that the biopsy has been taken from the wrong place.

The dangers of the biopsy are often discussed. Theoretically it might well be a means of spreading a malignant tumor owing to the opening up of blood vessels and lymphatics. In actual practice this danger appears to be negligible. In the largest surgical clinics where biopsies are done all the time the percentage of metastases is certainly no higher than when this method is not used. F. C. Wood performed biopsies without any special precautions on a large number of rats with carcinoma, and an equal number were left untouched. At the end of some months the animals were killed, and no difference in number of lung metastases was found in the two sets of animals. No one is afraid of using the diagnostic curettage where there ought to be every chance of spreading the malignant cells. The biopsy should be used more, not less.

Technical methods also differ. In some clinics reliance is placed on the examination of fresh unfixed tissue by frozen sections. Other pathologists prefer to wait for a paraffin section on fixed tissue. The writer's opinion is that the rapid method of examining the tissue by frozen sections is invaluable. The patient is still under the anesthetic, and when the report is given in the course of a minute or two the operation can be continued on conservative or on radical lines depending on the nature of the report. Sometimes, though rarely, one is unable to give an opinion from a frozen

section. The surgeon must then wait twenty-four hours for a report on a paraffin section.

Aspiration biopsy has proved useful in some hands. An aspiration needle of wide bore is inserted through the skin into the tumor; a minute quantity is aspirated and smeared on a slide. The pathologist has to familiarize himself with the microscopic picture before his opinion is of any value. The method has been used with success in carcinoma of the lung.

INNOCENT AND MALIGNANT TUMORS

There are two great classes into which tumors may be divided, the innocent, simple, or benign, and the malignant. The typical examples can be differentiated at a glance. Between these two extremes, however, there are intermediate grades, especially in the connective tissue tumors, which render a hard and fast line of demarcation impossible. It is not possible at present to say whether an innocent tumor ever becomes converted into a malignant one. Certainly the clinical evidence points that way, as in the transformation of a papilloma of the skin, bladder, or rectum into a carcinoma, a pigmented mole into a melanotic sarcoma, or an apparently innocent fibroid of the uterus into a malignant tumor, but it is more than possible that these tumors have been really malignant in type from the beginning, and are merely entering on a period of increased activity.

A malignant tumor differs from an innocent one in the following particulars:

1. It kills the patient wherever it may grow. An innocent one is only dangerous to life when growing in some vital part, such as the brain or larynx.

2. It infiltrates and destroys the surrounding parts. An innocent tumor merely pushes them aside, compressing them so that a capsule is formed. An angioma, however, may infiltrate widely.

3. It sets up secondary growths or metastases in neighboring lymphatic glands and in distant parts of the body, being spread by the blood stream or the lymphatics.

4. It tends to recur locally after removal. This, however, is merely because the removal has not been sufficiently wide.

5. It fails to approximate in character to the tissue from which it grows, rather resembling, especially in the connective tissues, the embryonic type. The innocent tumor reproduces the normal adult structure.

6. It usually shows mitotic figures. These are very rare in innocent tumors.

7. Its growth is usually rapid. It may however be very slow.

The nuclear viscosity of malignant cells is fundamentally different from that of normal cells (Cowdry and Paletta). When tissue is centrifuged at a high rate of speed the nucleoli and the chromatin are displaced when the viscosity is low. The viscosity is high in normal epidermis, lower in skin treated with a chemical carcinogen, and very low in skin cancer as well as in embryonic cells.

SPREAD OF TUMORS

An innocent tumor grows by expansion, much as a football grows when filled with air. A malignant tumor may spread in three ways: (1) by infiltration, (2) by embolism, and (3) by transplantation.

1. **Infiltration.**—This may occur in three ways.

(a) *Infiltration into Tissue Spaces.*—The tumor cells extend outwards between the planes of fascia, between muscle fibers and fat cells, and the mass comes to assume in consequence a very irregular form.

(b) *Permeation of the Lymphatics.*—When carcinoma cells enter a lymphatic they may grow along it, a process known as permeation. This is most readily recognized in perivascular, perineural and peribronchial lymphatics. The tumor cells distend the lumen of the vessel as by an injection, presenting a striking and characteristic appearance (Fig. 44).

(c) *Intra-epithelial Spread.*— This is an uncommon form of spread in which the cancer cells permeate a solid sheet of epithelial cells like the epidermis. It is best seen in Paget's disease of the breast, where the cells of a duct carcinoma make their way between the epithelial cells of the overlying skin.

2. **Embolism.**—Emboli of tumor cells may be carried by the blood stream or the lymphatics when the growth has invaded the respective vessels. Gray has made a valuable contribution to the study of the lymphatic spread of carcinoma by means of injection methods. Thorotrast, a colloidal solution, when injected into the lymphatic vessels can be detected not only by reason of being radio-

Fig. 44.—Carcinoma cells growing along a skin lymphatic. × 125.

paque, but also in microscopic sections by its negative affinity for most stains. The lymphatics are readily permeable to colloidal particles, and in the presence of inflammation erythrocytes rapidly enter these vessels in large numbers. It is evident that cancer cells lying in the tissues can easily enter the lymphatics, especially if they are ruptured by massage, although this is not equally true of blood vessels. Spread of cancer cells takes place first by embolism, as the flow of lymph is continuous and fairly rapid. When stagnation of lymph flow occurs, spread may take place by lymphatic permeation with the formation of secondary cutaneous cancer nodules. It would appear that for operable cases embolism is the only important method of lymphatic spread. The tumor cells when arrested in lymph nodes form secondary growths or *metastases.*

When carried by the blood stream the tumor emboli settle down in distant organs where they form metastases (Fig. 45). The lungs for the systemic, the liver for the portal circulation, are naturally the two organs most frequently involved. It is often very difficult to explain the distri-

bution of metastases. Organ predilection may play an important part. Although large numbers of emboli must lodge in the muscles, yet they do not produce secondary growths. They must be killed off, or fail to find a suitable environment. Long ago M. B. Schmidt observed in autopsy material that many tumor cell emboli in the lungs never developed into metastatic tumors. They became coated with fibrin, and the flow of blood, together with the constant motion of the lung during respiration, prevented the tumor cells from becoming implanted. Wood has shown that a few minutes' gentle massage of an animal tumor on two or three days greatly increased the number of pulmonary metastases. The following experiment offers striking corroboration of Schmidt's earlier observations. Two animals with the same type of tumor are massaged; one is killed at once, the other after a lapse of several months. In the former the lung capil-
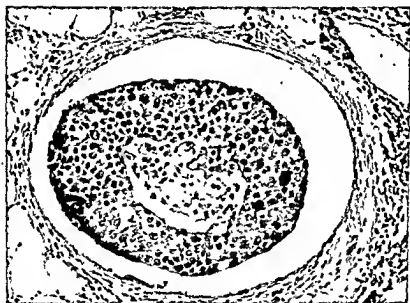
Fig. 45.—Embolus of tumor cells lying within a blood vessel. × 175.

laries were stuffed with tumor cells; in the latter only two or three metastases had developed. The numerous tumor emboli had evidently failed to develop and had died. Sometimes one tissue is picked out in a remarkable manner. Thus cancer of the prostate, breast, lung, thyroid, and kidney tends to set up widespread secondary growths in bone. Some organs, such as the heart and spleen, although provided with an abundant blood supply, are seldom affected by either primary or secondary tumors.

Metastases are not always found in those organs where they might be expected on strictly anatomical grounds. Cancer of the prostate may metastasize to the cervical vertebrae and to the long bones although no secondary tumors may be present in the lungs. Paradoxical embolism through a patent foramen ovale and other fanciful explanations have been suggested to account for this phenomenon. The work of Batson ap-

pears to provide the true explanation. By means of injections followed by radiography Batson has demonstrated a system of veins, which he names the vertebral system, passing up 'inside the spinal canal and anastomosing with sacral, lumbar, abdominal and thoracic veins, as well as with veins penetrating the vertebral bodies and cranial bones and cavity (Fig. 46). In animal experiments it was possible to show that there were frequent reversals of flow in this vast intercommunicating system, the result of coughing, straining, and increase of intra-abdominal pressure. During these reversals a pathway up and down the spine exists which does not involve the heart and lungs, a system which is more a venous pool or bypass rather than a vein with a constant flow of blood. As flow takes place into the system during coughing, it is easy to understand the high incidence of cranial metastases in cancer of the lung and

secondary brain abscesses in lung abscess. There are thus four systems of veins by which tumors may spread to a distance: the caval, pulmonary, portal and vertebral veins.

Roberts has drawn attention to a posterior or dorsal spinal lymph path by which tumor cells may pass up or down for considerable distances. This is formed by lymph vessels lying deep to the lumbodorsal fascia, which are supposed to be opened up as the result of obstruction to lymph nodes by metastases. This conception has been used to explain the upward passage of tumor cells from the prostate and the downward passage of cells from the breast. It is possible that this idea may be invalidated by Batson's work.

3. **Transplantation.**—This is not a common method of spread, but·in a serous cavity the route by which the *tumor cells have been carried from* one place to another may be very

Fig. 46.—Vertebral system of veins and its connections. (Batson: Ann. Surg., 1940, *112*, 138.)

evident. In one case of cancer of the stomach there were large secondary growths in both ovaries (Fig. 327, page 501), and the intervening peritoneum was studded with small nodules similar in structure to the growth in the stomach and ovaries. Undoubted cases have occurred in which a tumor of the lower lip has been transferred to the upper, or one of the cervix to the opposite wall of the vagina.

Inoculation is one variety of transplantation. It is well recognized by surgeons that if a tumor be cut into during the course of its removal there is danger of infecting the surrounding tissues and the skin. That the danger of biopsies as a cause of embolism has been overestimated is shown by the observations of Wood described on page 107. At the same time the surgeon must remember that there is no more effective method of breaking down local resistance than by cutting through the capsule

Fig. 47.—Grade 1.

Fig. 48.—Grade 2.

Fig. 49.—Grade 3.
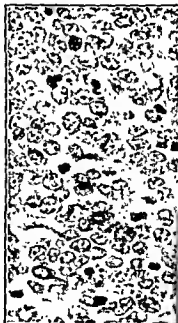
Fig. 50.—Grade 4.

Figs. 47 to 50.—The four grades of epidermoid carcinoma. Differentiation is complete in Fig. 47; Fig. 50 is extremely anaplastic with many mitotic figures. Fig. 47, × 200, Figs. 48 to 50, ×500. (Author's A Textbook of Pathology, Lea & Febiger.)
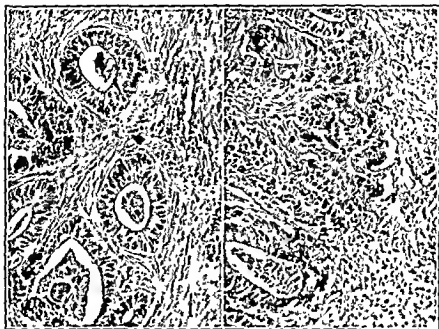
Fig. 51.—Grade 1. Fig. 52.—Grade 2.
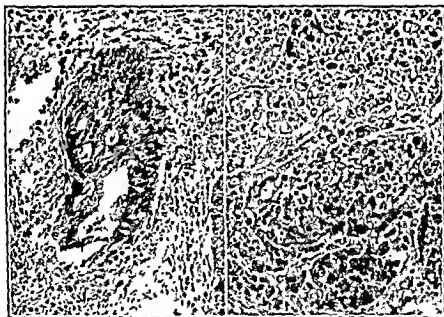
Fig. 53.—Grade 3. Fig. 54.—Grade 4.

Figs. 51 to 54.—The four grades of adenocarcinoma. × 125. (Author's A Textbook of Pathology, Lea & Febiger.)

of a tumor and into its substance. One frequently sees very rapid growth of a tumor after an unsuccessful attempt at removal. Kettle records an interesting example of implantation where an exploring needle was passed into an adenocarcinoma of the liver, and a few months later a nodule

with the same structure appeared in the skin at the site of puncture. A particularly convincing example of transplantation is afforded by a case reported by Brandes et al. Several months after mastectomy for a highly malignant carcinoma of the breast cancer nodules developed on the opposite thigh over the area from which a skin graft had been taken to cover the site of operation. The instruments and drapes had been changed after removal of the breast tumor, but not the surgeon's gloves.

The question of the spread of tumors is obviously one of great importance to the surgeon. Those desiring more detailed information should consult Willis: *The Spread of Tumors in the Human Body*, which is a storehouse of interesting and valuable information.

THE GRADING OF TUMORS

Malignant epithelial tumors can be divided according to their microscopic appearance into different grades of malignancy, the least malignant being classed as Grade 1, and the most malignant as Grade 4, using Broder's system of classification (Figs. 47–54). The principal factors to be observed in grading a carcinoma are: (1) the degree of differentiation, (2) the character of the cells and nuclei, and (3) the number of mitotic figures. The more complete the differentiation, the less malignant is the growth. In a tumor of glandular tissue the completeness with which approximately normal gland structure is reproduced is the criterion, whilst in a squamous cell cancer of the skin attention is paid to the amount of cornification. Complete lack of differentiation (a high degree of anaplasia) indicates rapid growth and marked malignancy. Great variation in the size and shape of the cells and hyperchromatic (darkly staining) nuclei point in the same direction. Other things being equal the more numerous the mitotic figures, the more malignant is the growth. It will be observed that these criteria are cytological as well as histological. MacCarty has emphasized the importance of study of the individual cells, especially in material which has not been altered too much by fixation and dehydration. As he points out, a feature of special importance is the relatively large size and prominence of the nucleolus in the malignant cell, which in this respect resembles the normal nerve cell. From the pathological standpoint there is, of course, nothing new in distinguishing between different degrees of malignancy in a tumor, for it was in 1893 that Hasemann first introduced the concept of anaplasia.

The surgeon must remember that, from the point of view of prognosis, there are other points of even greater importance than the microscopic appearance of the tumor. In what may be called clinical grading one must consider the age of the patient, the duration and size of the tumor, its rate of growth, the presence of metastases, and the general appearance of the patient. The chief value of microscopic grading is not in relation to prognosis but in determining the degree of radiosensitivity of the tumor although here also it is necessary to take other factors into consideration.

THE RADIATION OF TUMORS

General Principles.—Two main forms of radiation are used in the treatment of malignant tumors; these are radium and X-rays. Radium may be used in the form either of radium element or of radium emanation (radon).

The latter is a heavy radio-active gas given off continuously by radium and belonging to the helium group; it differs fundamentally from radium in that it loses 50 per cent of its initial activity in the first four days. Both radium and radon give off three forms of rays known as alpha, beta and gamma rays. The alpha and beta rays are not true rays in the sense of waves, but are very rapidly moving particles highly destructive in their effect on normal tissues, as well as on tumor cells, and therefore undesirable in therapeutic work. The gamma rays are true electromagnetic vibrations like X-rays and light and heat waves. The penetrating powers of the alpha, beta and gamma rays are respectively 1 : 100 : 10,000. Advantage is taken of this fact in screening off the rays which are not wanted. The highly destructive alpha rays (or particles) are so readily absorbed that they are stopped by the thickness of a sheet of paper, and

Fig. 55.—Secondary deposits of a squamous carcinoma in a lymph node, showing a considerable degree of necrosis as the result of radiation, together with marked fibrosis.

therefore never escape from the radium container. The beta rays can also be filtered out, leaving the all-important gamma rays to act alone. The gamma rays have a remarkably selective action compared with the alpha and beta rays. The latter produce a diffuse cytocaustic effect, the various components of the tissue exposed being all affected to the same degree, so that the result is a general necrosis with severe burning of the skin. The highly penetrating gamma rays, on the other hand, produce what Regaud calls a selective cytolethal action without any burning of the skin provided a correct dose is employed.

Radiation may be used, at present in three ways: (1) external radiation (X-rays or radium in the form of a bomb); (2) surface application of radium in the form of a plaque; (3) interstitial radiation by means of radium needles. The needles may contain the radium itself, or the radium emanation (radon). The various methods are used for different kinds of

tumor and for tumors in special positions. For widespread tumors such as lymphosarcoma X-rays are the most useful. A fully differentiated epidermoid carcinoma is unaffected by X-rays, but may be attacked by interstitial radiation (Fig. 55).

The *biological effect* of the gamma rays of radium appears to be identical with that of X-rays. Much of the initial work was done on animals, but it is important to note that there is a marked inconsistency between the results of animal experiments and those of clinical experience. For instance when a mouse affected with carcinoma is radiated, the tumor being completely protected from the rays, the carcinoma may disappear. In man nothing like this happens. If it did, we would have a potent means of dealing with metastases.

The *principles of radiosensitivity* are at present only dimly understood but they are of supreme importance. As long ago as 1904 Bergonie and Tribondeau formulated a law which may be called the biological foundation for radium and roentgen ray treatment. It is as follows: "Immature cells and cells in an active state of division are more sensitive to irradiation than are those that have acquired adult morphological and physiological characteristics." Carcinoma in some organs is on the whole radiosensitive (skin, mouth, cervix), whilst in other organs it is equally resistant (stomach, rectum). Speaking generally, epidermoid carcinoma is sensitive, whereas adenocarcinoma is resistant. A cell is not radiosensitive when it is in a condition of good secretory activity (Regaud). Cancers which induce an abundant growth of connective tissue (scirrhous carcinoma of the breast) are markedly resistant. At present the most convenient means of determining the degree of radiosensitivity is by observing the amount of differentiation or lack of differentiation (anaplasia) which it displays. Thus, if an epidermoid carcinoma resembles adult differentiated tissue with cornification and pearl formation, it will be resistant, whilst the more anaplastic it is, the more sensitive to radiation it will be. Grade 1 carcinoma is therefore resistant, and Grade 4 carcinoma highly sensitive. There are important exceptions to the general rule that anaplasia and rapid growth indicate marked radiosensitivity. The highly malignant form of glioma known as glioblastoma multiforme, malignant melanoma, and neurogenic sarcoma may all be very anaplastic and yet they are markedly radioresistant. On the other hand rodent ulcer, a slowly growing tumor with few mitotic figures, is very radiosensitive. Tumors of embryonic origin (embryomas) are highly radiosensitive. The phase of cell life which is most easily damaged by radiation is the phase of mitotic division. For this reason a tumor showing numerous mitotic figures will respond well to radiation. It is important, however, to distinguish between radiosensitivity and curability. A highly anaplastic tumor will respond wonderfully well locally, but its high degree of malignancy makes it probable that early dissemination has occurred, so that the patient may die in spite of successful treatment. No tumor is more radiosensitive than lymphosarcoma, where the tumor mass may melt away like a snowball before the fire, but involvement of deep and distant glands will too often defeat the best efforts of the radiotherapeutist. Radiations appear to inhibit mitosis, preventing the cells from dividing. In this way they may completely arrest the growth of a tumor for a considerable period without destroying it.

Effects of Radiation.—The importance of the selective action of radiations has already been emphasized. Without such selectivity radiation therapy would be impossible. The action on the tumor must be different both in degree and kind from the action on the tumor bed (the tissues). These two actions must therefore be considered separately.

1. *Action on the Tumor.*—When a highly radiosensitive tumor such as lymphosarcoma or Ewing's tumor of bone is radiated cytolysis occurs with remarkable rapidity, so that liquefaction of the cell may occur in the course of a few hours, and the tumor may literally melt away. Necrobiosis of the cell occurs, with fragmentation or chromatolysis of the nucleus and vacuolation and liquefaction of the cytoplasm. This process can be watched to best advantage in a tissue culture of a tumor, as may be seen on the screen in the incomparable Canti film. Mitotic nuclei are particularly vulnerable, so that cells undergoing mitotic division and those rich in nuclear chromatin respond with the greatest readiness. The radiation exerts a selective action, the more immature and embryonic cells suffering to the greatest degree. A basal-cell carcinoma of the skin (rodent ulcer) is therefore much more severely damaged than the squamous form of epidermoid carcinoma.

Two different types of effect may be produced, depending on the way in which radiation is used. (1) *Autolytic degeneration* and softening. This is the most desirable effect and may be observed in highly radiosensitive tumors of anaplastic type (lymphosarcoma, Ewing's tumor of bone). The changes are those which have just been described. By appropriate screening it is now possible to produce similar results in less anaplastic tumors, such as carcinoma of the mouth, tongue, tonsil and the cervix uteri (Fig. 55). The caustic and destructive effects formerly produced in these tumors by unfiltered rays are to be avoided. (2) *Growth restraint* may be produced in tumors which in themselves are not specially radiosensitive, *i. e.*, osteogenic sarcoma of bone and adenocarcinoma of the body of the uterus. Although these tumors are not destroyed, growth may sometimes be inhibited to such a degree that subsequent surgical removal may be attended with better chances of success. It would appear in these cases that the action of radiation is to prevent the cell from entering the mitotic phase.

2. *Action on the Tumor Bed.*—Radiation acts as an irritant to the tissues, so that an inflammatory exudate of serum and cells is formed. At first the cells are polymorphonuclear leucocytes, but these are replaced later by lymphocytes, plasma cells and eosinophils, all of which seem to play a part in the defense reaction. The cellular exudate is most pronounced in persons with marked resistance to the tumor. A fibroblastic reaction occurs later, the fibroblasts lay down collagen fibrils, and the final result is a dense fibrosis. The blood vessels show a marked reaction, and the local obliterative endarteritis which results greatly diminishes the blood supply to the part. Thrombosis is a common accompaniment. Fat is highly resistant to radiation, but after heavy dosage the cell membranes rupture, oil cysts form and saponification occurs. Fat forms a poor defence against cancer cells, which grow into the fat and are there shielded from the radiation. Hence the poor results of radiation of the axillary fat in cancer of the breast. When cancer invades bone it becomes

radioresistant, although it may have been highly radiosensitive before. This will be seen in the case of rodent ulcer. The danger in repeated radiation of bone is the production of a chronic radiation osteitis which makes the bone hard and brittle and liable to spontaneous fracture. It is evident that the nature of the tumor bed must be taken into account in considering the advisability of radiation therapy in any given case; too often the tumor alone is considered. Heavy infection of the tumor bed is an important contraindication for treatment by radiation, as the resistance of the tissues is seriously impaired, and radiation may cause severe and fatal sloughing. This is particularly dangerous in the case of a hollow viscus such as the rectum. It is therefore of the greatest importance to reduce the element of infection to a minimum in such a tumor as carcinoma of the rectum, by means of a preliminary colostomy, before employing radium.

Radionecrosis is the term applied to necrosis of the healthy tissue produced by overdosage. If the dose is very large, there is immediate necrosis with sloughing, and the resultant defect will never heal. If the dose is smaller, the greater part of the lesion will heal, but a small area of necrosis may remain. If the overdosage is only slight, healing will be complete, but the tissue may readily break down again as the result of infection or trauma, for the resistance of radiated tissue is seriously impaired owing to progressive endarteritis. I have seen tissues break down as long as eight years after radiation. Correct estimation of dose is therefore all important in radiation therapy. "The aim of all modern radiotherapy is to eliminate indiscriminate caustic action, and by adequate filtration and graduated exposure to administer such doses as shall have the maximum destructive effect upon neoplastic cells with the minimum, of dosage to normal tissues" (Colwell).

Precancerous Lesions.—The idea of precancerous lesions, lesions which although not in themselves malignant yet strongly predispose to malignant neoplasia, has been growing in favor during the last fifty years. There is much to be said in favor if it, but there are some serious objections against it, and the question is by no means settled. The arguments in favor are mostly clinical, the objections are mainly pathological. The supposed precancerous conditions may be divided into a number of groups.

Chronic inflammation precedes cancer in a large number of cases. This is well seen in the skin, in the gall bladder, in the uterus, and elsewhere. But are we justified in calling the inflammatory lesions precancerous in the sense that they are a half-way house between a normal and a malignant condition? It appears rather to be a case of the long-continued action of an irritant which is generally admitted to be one of the most important exciting causes of malignant disease. In the mouth the evidence is rather more convincing, for the leukoplakia, warts, and fissures which characterize syphilis of the tongue not only often develop into carcinoma, but show an epithelial hyperplasia and papillary downgrowths which are suggestive of the commencement of a malignant process. Similar changes are seen in the mouth as the result of the irritation of excessive smoking and of ragged teeth. The rôle of gastric ulcer as a precancerous condition is discussed on page 232. Undoubtedly some

cases of carcinoma do arise on the basis of a simple ulcer, but it is probable that such an occurrence is quite uncommon.

Physiological involution is sometimes regarded as a precancerous condition, especially in the breast and prostate. The arguments in favor of the idea are marshalled by Ewing. This question will be taken up in detail when cancer of the breast and prostate are considered. It may, however, be pointed out here that the frequent association of carcinoma with chronic mastitis and hypertrophy of the prostate does not in itself constitute an argument of weight. These are involutionary conditions which naturally occur in the later period of life. Cancer is also a disease of this period, owing to the long time that the causal agent needs to operate. The association of the two conditions is therefore largely coincidental. The senile keratosis of the skin seen in seamen and others much exposed to inclement weather not infrequently become malignant, a more significant occurrence, it appears to the writer, than the association of carcinoma with chronic mastitis and prostatic hypertrophy.

The *transformation of benign into malignant tumors* is another matter regarding which there is much difference of opinion. In most situations it is probably an occurrence of great rarity. Carcinoma of the breast, for instance, is much more likely to develop from non-tumorous breast tissue than from a pre-existing fibroadenoma. In the uterus the change of a fibromyoma into a sarcoma must be admitted. The best example, however, is provided by the papillomata or polypoid adenomata of the stomach, intestine, and bladder. In the colon and rectum in particular multiple papillomata have a strong tendency to become malignant. Lockhart-Mummery has drawn attention to the three stages through which the mucous membrane of the rectum may pass. First, there are localized patches of hyperplasia, invisible to the naked eye, affecting *an extensive area of the bowel. Secondly, a crop of adenomata appear* over this area of hyperplasia. Thirdly, the development of carcinoma in one of these adenomata. These changes are well illustrated in one of my own cases (Fig. 200).

Fig. 56.—Carcinoma in situ in gastric mucosa. × 40.

The clinician uses the term "precancer" to include conditions in which cancer is only a probability or even a possibility. To the pathologist, on the other hand, it should mean rather a local "unrest" of cells which often precedes infiltration by cancer, a disordered and invasive epithelial growth without actual infiltration of the deeper structures. Such a change may be seen most typically at the margins of carcinomas, possibly indicating a radial transmission of cancerous activity to cells not originally involved.

Broders has introduced the convenient term *carcinoma in situ* to indicate a condition in which the epithelium shows definite cytological malignant change such as marked variation in the size and character of

the cells, hyperchromatism, mitoses, etc., yet there is no invasion of surrounding tissue (Fig. 56). In time, of course, such invasion is bound to occur. Experimental work serves to show that tissue may be marked for malignant change and yet show no microscopic evidence of this fact. If an area of skin is tarred for a certain time, and the tarring then stopped, a biopsy may show absolutely no change, and yet a month later there may be clinical and microscopic evidence of malignancy. The biopsy specimen was in the primary phase of carcinogenesis, the phase of preparation which is necessary before the sudden change that converts potentially malignant into malignant cells.

Prognosis in Cancer.—It is extremely difficult to assess the prognosis in different forms of cancer. This is due to many causes, perhaps the chief of which is the lack of uniformity in method of reporting end results in different clinics. Much depends on what is meant by a cancer cure. The stage at which the disease is first treated is the most important single factor in determining the result. If only those cases which can be followed up for five years are included, the results will naturally be much more favourable than if all treated cases are included and those of which all trace is lost are presumed to have died of the disease. Recent reports give a more cheerful picture than those of some years back owing to advances in methods of treatment, particularly in radiotherapy. An excellent summary of the results of the treatment of all the common forms of cancer will be found in Nathanson's paper.

CLASSIFICATION OF TUMORS

It is safe to say that there is at present no satisfactory classification of tumors. Nor, indeed, is such a classification possible with our present knowledge. The classification which will be used here is merely a working classification based on the type of tissue from which the tumor originates, but as in many cases it is difficult or impossible to say what that tissue is, the method is far from ideal.

Tumors for our present purpose may be arranged as follows:

1. Connective tissue tumors.
   A. Innocent
      - Fibroma.
      - Lipoma.
      - Myxoma.
      - Chondroma.
      - Osteoma.
   B. Malignant. Sarcoma.
2. Muscle tissue tumors
   - Leiomyoma.
   - Rhabdomyoma.
3. Epithelial tumors.
   A. Innocent
      - Papilloma.
      - Adenoma.
   B. Malignant. Carcinoma.
4. Nervous tissue tumors. Glioma.
5. Endothelial tissue tumors
   - Endothelioma.
   - Hemangioma.
   - Lymphangioma.
6. Pigmented tumors
   - Nevus.
   - Melanoma.
7. Chorionepithelioma.
8. Teratomata.

FIBROMA

A fibroma is a tumor composed of fibrous tissue. It consists of fibroblasts with a varying amount of intervening fibers. It varies greatly in consistency, and two types are commonly described, the hard and the soft, but all intermediate grades may be met with. Considering the wide distribution of fibrous tissue it is somewhat remarkable that fibromata are not common. As a matter of fact a pure fibroma is a very rare tumor.

The *hard* fibroma is globular in outline, but may be lobulated. It is easily separated from the tissue from which it arises. When cut there is a peculiar creaking sensation as of cartilage. The cut surface is flat or slightly convex, white in color, and intersected by glistening bands.

Microscopically it consists of bundles of white fibers cut in different planes, between which are small elongated nuclei representing the flattened connective tissue cells. The vessels are small and few in number, but may be large and thin-walled. In the latter case they may be unable to collapse, so that there may be free hemorrhage when the tumor is cut into.

The *soft* fibroma displays no glistening surface. It consists of loose areolar tissue, the slender bundles of which form an open network sometimes containing abundant fluid.

Fibromata may occur in almost any part of the body, but the usual sites are the skin, mucous membranes, muscles, bone, nerves, and certain of the viscera.

Skin.—A fibroma may occur as a *hard nodule in the skin or subcutaneous tissue.* Soft fibromas, often pedunculated, are called molluscum fibrosum, but are really tumors of cutaneous nerves.

Fig. 57.—Keloid; excessive scar formation.

Keloid or cheloid is not a true tumor, but a tumor-like condition which generally originates in a scar (Fig. 57). It is a firm, smooth, pink or reddish, raised patch from which extend claw-like processes, and it may come to cover a considerable area. Some persons have an idiosyncrasy to the development of keloid, and it is common in Negroes. It consists of very dense fibrous tissue, the bundles of which run parallel with the surface. It tends to recur when removed.

Dermatofibroma.—This is a small, hard, circumscribed, non-encapsulated growth in the corium, with a maximum size of 1 to 1.5 cm. The common site is the extremities. It is composed of large, irregular, fusiform

cells running in many directions and interlacing. It may be highly cellular and have abundant collagen and few cells. An important feature is the ill-defined margin with infiltration of the surrounding tissue. It is commonly mistaken, clinically, for melanoma and neurofibroma. The microscopic picture is easily confused with that of neurofibroma, but there is absence of palisading of the nuclei, lack of capsule, and the tumor is in the corium, not the subcutaneous tissue (Fig. 58). The histological features are well shown in Stecker and Robinson's paper, which reports 60 cases.

Mucous Membranes.—The fibroma arises in the submucous coat, and often becomes pedunculated. It occurs in the esophagus, stomach, and intestines. In the latter position it may cause intussusception.

Muscles.—The only example of importance is fibroma of the abdominal wall. This comparatively rare tumor arises from the fascia of the rectus sheath, and tends to infiltrate the muscle. It is densely hard, and the cut surface shows interlacing bundles of white fibrous tissue. Stewart and Mouat have pointed out that the muscle fibers enclosed in the tumor

Fig. 58.—Dermatofibroma. × 12.

undergo a peculiar reversionary change, resulting in the formation of multinucleated plasmodial masses resembling foreign-body giant cells. About 80 per cent of the cases occur in women who have borne children, owing probably to the physiological trauma of labor. In the remaining cases occurring in men and in women who have not borne children, there is usually a history of trauma to the abdominal wall. In rare cases the tumor occurs in the scar of an old abdominal operation.

Bone.—Fibromas of bone are rare, and frequently prove to be fibrosarcomas. A fibrous polypus may grow from the nasopharynx, and extend into the Eustachian tube or the orbit. A fibrous tumor growing from the alveolus of the jaw is called a fibrous epulis, and must be distinguished from the giant-celled epulis to be described later.

Nerves.—Fibromas often grow from nerves (nerve sheath) and are then known as neurofibromata. They present special features which are considered in connection with nerve tumors (page 663).

Viscera.—A pure fibroma is occasionally found in the ovary as a hard mass which may attain a considerable size. In the kidney there may be small, hard, fibrous nodules in the cortex or the medulla.

Fibrous tissue is often a prominent feature in adenomata of the breast and myomata of the uterus, but it does not form an essential part of the new growth, although it may modify its character very considerably.

Xanthoma.—This is a name applied to a group of conditions rather than to a single type of tumor. Three distinct forms may be recognized. (1) Xanthelasma, by far the commonest variety, characterized by multiple small yellow patches in the inner part of the eyelids. They occur in persons over middle age and represent a degenerative process in the muscle of the lid. (2) Xanthoma multiplex, a condition in which groups of yellow nodules are scattered over the trunk and extremities, occurring in young people, and associated with a disturbance of cholesterol metabolism, a hypercholesterolemia, or with a lipemia. It is therefore met with in diabetes mellitus and in biliary obstruction. (3) A heterogeneous collection of xanthomatous masses, many of which are fibromas of the tendon sheaths of the hand and less frequently of the feet, some of which are classified by Bloodgood as fibrohemangiomas, and yet others which are associated with infections or trauma and which are of the nature of granulomata rather than true tumors.

All of the lesions display a characteristic bright yellow color which gives the condition its name. The source of this color is still a matter of dispute. Most authorities hold that it is due to the presence of the ester of cholesterol which is so constantly present. Garrett, on the other hand, maintains that it is due to blood pigment. The microscopic picture is characteristic. There is a deposit in the tissue of a finely divided lipoid substance, cholesterol ester, which is absorbed by connective tissue

Fig. 59.—Touton cells. × 500.

and endothelial cells. These become greatly distended, and the contained lipoid gives them a pale and "foamy" appearance like that of the cells of the adrenal cortex or a hypernephroma. In addition to these foam cells there are usually foreign body giant cells, numerous spindle connective tissue cells which are apt to give rise to a mistaken diagnosis of sarcoma, and blood pigment. In some cases a striking feature is the presence of so-called *Touton cells*, giant cells characterized by a remarkable ring of nuclei right round the periphery of the cell (Fig. 59). They may be very numerous. I have not met with them in any other condition.

It is evident that a "xanthomatous tumor" may be more of a granuloma than a neoplasm. Xanthomatous changes may, however, be met with in giant-cell tumors of bone and other connective tissue tumors.

LIPOMA

A lipoma (Fig. 60) consists of normal fat arranged usually but not always in irregular lobules separated by fibrous septa. It is surrounded

by a delicate capsule of connective tissue, and is very readily shelled out. It may grow to any size, and often becomes pedunculated. It is one of the most innocent of tumors, but on rare occasions a malignant form (lipo-

Fig. 60.—Lipoma. The encapsulated character of this growth is well shown.

sarcoma) may be encountered. A liposarcoma is seldom seen before the age of 50; it tends to recur and form metastases, but the latter are very late in appearing. The microscopic picture of the malignant tumor is mixed, consisting of islands of embryonic fat, adult fat, and myxomatous stroma, but the predominant tissue is compact spindle cells sometimes associated with immense tumor giant cells with foamy cytoplasm (Fig. 61). The embryonic fat cell resembles a small liver cell with abundant granular cytoplasm. These granular or finely vacuolated cells may sometimes be seen in an ordinary lipoma, and occasionally the tumor is composed entirely of these cells.

Fig. 61.—Liposarcoma, showing giant cells. × 520. -

The common site is the subcutaneous tissue, especially of the neck, shoulders, back, and buttocks. It may occur in the mesenteric and retroperitoneal fat, and rarely in the submucous coat of the stomach and intestines.

The so-called "diffuse lipoma," generally met with in the neck, is not a true tumor. It merges with the surrounding fat.

A lipoma can be diagnosed from the following characters. It forms a soft, painless, usually lobulated mass, the overlying skin being often slightly dimpled owing to fibrous bands passing from it down between the lobules. It moves readily over the deep fascia, and can be distinguished from a collection of fluid in that it possesses a very definite margin which can be felt through the skin.

Although lipomas are usually single they may occasionally be multiple, and are then easily mistaken for multiple neurofibromas. A differential point of value is that a lipoma tends to be colder than the surrounding tissue to the palpating hand, owing to absence of blood vessels.

MYXOMA

A true myxoma is one of the rarest of tumors. On the other hand mucoid degeneration is of common occurrence in many connective tissue tumors such as fibromas, chondromas and sarcomas. The mucous polypus of the nose bears no relation to a myxoma. Indeed it is not a neoplasm at all, but a mass of edematous inflammatory tissue, jelly-like in consistence, and containing mast cells and eosinophils.

Microscopically a myxoma resembles Wharton's jelly or the vitreous humor of the eye in structure. It consists of a delicate reticulum of branched connective tissue cells, in the meshes of which there is an abundant mucinous fluid, which becomes granular on the addition of acetic acid, and can be stained differentially with muci-carmine.

A myxoma occurs in the same positions as fibromata. It is perfectly encapsulated and is readily shelled out. A tumor diagnosed as a myxoma on removal not infrequently proves later to be a sarcoma.

CHONDROMA

A chondroma is a tumor consisting of cartilage, firm in consistence, bluish-grey in color, and with a somewhat translucent surface. When

Fig. 62.—Chondroma, showing irregular character of cells. × 100.

growing to any size it is usually lobulated, and possesses a well-marked capsule, so that it can be readily shelled out.

Microscopically it presents the appearance of normal cartilage, but the cells do not as a rule have so regular an arrangement (Fig. 62).

It grows in connection with bones, and is also met with in mixed tumors of glands, usually malignant in character.

Containing practically no vessels and deriving its nourishment only from the vessels in the capsule, it is peculiarly liable to myxomatous and calcareous degeneration in the central parts.

The parts chiefly affected are the ends of the diaphysis of the long bones, especially in young people, where ossification is common, the metacarpals and phalanges of the hand, often multiple, where ossification is rare, and the bones of the thorax and pelvis, where they may attain a large size and cause serious obstruction of the cavity.

Mixed tumors of the testicle, the parotid and submaxillary glands, and rarely the breast, may contain such a large proportion of cartilage as to present the appearance of a pure chondroma.

OSTEOMA

A true osteoma is a somewhat rare tumor. New formations of bone are of common occurrence, for example the callus at the site of a fracture, the masses of bone which may be formed in a muscle as the result of injury, the formations around joints, the seat of chronic arthritis, etc. These, however, are not examples of tumor growth.

As bone consists of two varieties, the cancellous and the compact, so also may osteomas be similarly divided.

The *cancellous osteoma* occurs in young growing subjects at the end of the diaphysis close to the epiphyseal line, although with the growth of the bone the distance from that line may become greater. It almost certainly originates as a piece of the epiphyseal cartilage which has become separated and then ossified. It is usually pedunculated, and covered at the growing tip by a cap of cartilage. Unless this cartilage is removed when the tumor is operated on it will recur. The usual site is the lower end of the femur or the upper end of the tibia.

The *subungual exostosis* is a variety of cancellous osteoma which grows from the dorsum of the distal phalanx of the big toe. It causes intense pain through raising the nail, finally causing it to break away.

The *compact osteoma*, often called an ivory exostosis, is an extremely hard sessile tumor usually growing from the vault of the skull. It occasionally originates in the frontal or ethmoidal sinuses, from which it may invade the orbit.

SARCOMA

A sarcoma is a malignant tumor of connective tissue. The group as at present constituted is large, indefinite, and includes various members which have no rightful place there. Malignant tumors of muscle, lymphoid tissue, and pigment cells should be excluded, and the term strictly confined to tumors of connective tissue origin. This, however, is at present a counsel of perfection, for such a term as lymphosarcoma is so deeply rooted in the literature that it cannot easily be eradicated.

The histological diagnosis of sarcoma may be one of the most difficult tasks in pathology. A typical sarcoma can be recognized at a glance, but

there are numberless gradations towards the innocent connective tissue growths which may make differentiation very hard. To complicate the problem still further simple inflammatory tissue, especially when under-going repair, may bear so close a resemblance to certain forms of sarcoma as to deceive the very elect.

Degeneration is peculiarly liable to occur in a sarcoma, largely on account of the great rapidity of growth, which may outstrip the supply of nourishment. Hemorrhage is of such frequent occurrence, owing to the thin-walled character of the vessels, that its presence in a tumor should arouse suspicion of a sarcoma. It is attended by liquefaction of the tissue, and a spurious cyst is formed containing bloody fluid. Mucoid degeneration is common, and the tumor may be mistaken for a myxoma. Fatty degeneration and calcification may occur, and part of a tumor growing from bone may become ossified—the ossifying sarcoma.

Malignancy.—In the group of sarcomas are included some of the most malignant tumors which attack the body. On the other hand there are some which can with difficulty be distinguished from innocent fibrous tissue growths. Recurrent fibroid used to be a common diagnosis for tumors which when first removed appeared quite innocent, but which recurred again and again, and with each removal showed a more definite histological appearance of malignancy. Speaking generally, the less the differentiation the greater is the malignancy. The malignancy is evidenced in two ways, (1) by invasion, and (2) by the formation of metastases.

(1) The infiltrating powers of a sarcoma are notorious. A sarcoma of bone may infiltrate the surrounding muscles. A sarcoma of the maxilla may creep through all the foramina opening into the spheno-maxillary fossa and appear in the cranial cavity. A sarcoma of the kidney may invade the renal vein and climb far up along the vena cava. On the other hand it is remarkable how slender a barrier may stop the spread of the tumor. One of the best examples of this is afforded by a sarcoma of bone in the neighborhood of a joint, where the articular cartilage usually effectively prevents the invasion of the joint. The explanation probably lies in the absence of vessels in the cartilage.

(2) Metastases are both early and widespread. The tumor spreads by the blood stream, gaining ready access to the veins on account of the thin-walled nature of its vessels. As would be expected, secondary growths are commonest in the lungs, and in the liver in sarcoma of organs drained by the portal circulation, but the distribution may be more widespread. Spread by the lymphatics is much less common, but secondary growths may be found in the lymph nodes.

Naked-eye Appearance.—No general description is possible which will embrace all the varieties of sarcoma. Certain characters, however, would lead the observer to suspect the sarcomatous nature of the growth. A typical sarcoma, such as the round-celled variety, is soft in consistence, often closely resembling the white matter of the brain, of a greyish or pinkish white color, and presents a homogeneous appearance very different from the whorls of a fibroma or the cellular masses of a carcinoma. A spindle-celled sarcoma, such as that growing from the periosteum, may, however, have a distinctly striated appearance. Hemorrhage is frequent

as also are areas of necrosis and softening. The vessels supplying the tumor are usually large, although those in the stroma may be mere capillaries, so that alarming hemorrhage may occur if the tumor is incised during removal. There is no capsule.

Microscopic Appearance.—It used to be customary to classify sarcomas according to the size and shape of the cells, so that there were small or large round-cell sarcomas, spindle-cell sarcomas, etc. It is now recognized that there is probably no such thing as a round-cell sarcoma. The round-cell appearance is due either to poor fixation and staining or to the fact that the tumor is a lymphosarcoma, anaplastic carcinoma, medulloblastoma, etc. Connective tissue cells are not round. The spindle-cell sarcoma is composed of fibroblasts, and is now called a fibrosarcoma (Fig. 63). Even if the fusiform shape is but poorly marked, as in the old round-cell sarcoma, the tumor is still a fibrosarcoma. When sarcoma

Fig. 63.—Fibrosarcoma; large cells and greatly swollen nuclei. × 1000.

arises from cartilage it is called chondrosarcoma, from bone it is called osteosarcoma or osteogenic sarcoma, from fat it is called liposarcoma, etc. The tumor is highly cellular, and the stroma may be so scanty as to be almost invisible. The cells of a carcinoma are arranged in groups separated by a stroma usually abundant, but the stroma does not penetrate between the individual cells of a group, nor do the blood vessels. In these respects the tumor resembles the epithelium from which it arises. In a sarcoma, on the other hand, the cells are scattered uniformly throughout the tissue, and separated from one another by a delicate stroma in which run numerous thin-walled blood vessels. It is true that in the so-called alveolar sarcoma there is an attempted alveolar grouping of the cells in places, but in other parts the above description will be found to hold. In the more rapidly growing forms mitotic figures are numerous, and in all doubtful cases these should be carefully searched for. It must be remembered that in actively growing granulation tissue the fibroblasts may show occasional mitosis. The walls of the blood vessels are characteristically thin, and in many cases appear to be formed of little more than the cells of the tumor. It is easy to understand, therefore, the frequency both of hemorrhage and invasion of the blood stream.

Neurosarcoma (Neurogenic Sarcoma).—This is a variety of fibrosarcoma, arising from nerve sheaths. It is considered in connection with disease of the nerves. At first it is only of local malignancy, but when removed it tends to recur and may set up metastases in the lungs. The elongated cells show a marked tendency to be arranged in whorls with

fasciculi. It seems probable that most sarcomas of fibrous tissues belong to the neurogenic group.

Other Sarcomas.—*Osteosarcomas* and *chondrosarcomas* are conveniently considered in connection with diseases of the bones. The so-called *giant-cell sarcoma* will be considered in the same place. It is not a real sarcoma and is better called a giant-cell tumor of bone. Lymphosarcoma is a disease of the lymphoid structures, and will be considered in connection with that system. Although highly malignant, it is not a real sarcoma. A *melanotic sarcoma* is also not a true sarcoma, and is described under the heading of malignant melanoma.

Chordoma.—This very rare tumor of hypoblastic origin is described in connection with diseases of the spine.

MUSCLE TISSUE TUMORS

Corresponding to the two kinds of muscle, plain and striated, there are two varieties of tumors, leiomyoma and rhabdomyoma; the former is very common, the latter very rare.

LEIOMYOMA

Plain muscle tumors may occur wherever plain muscle is found, and small nodules are not uncommon under the capsule of the kidney, and in the wall of the intestine where they may form polypoid growths which hang into the lumen of the bowel. In these positions they hardly ever produce symptoms and are of no practical importance.

In the uterus, on the other hand, they are extremely common, and may produce symptoms of great gravity. Intermingled with the muscle cells there is a varying amount of connective tissue; on this account the tumor is known as a "fibroid." It is considered fully in connection with diseases of the uterus (page 468).

The myoma is an innocent tumor, consisting of bundles of plain muscle fibers (Fig. 64), but occasionally it may take on malignant characters. The muscle fibers and their nuclei become swollen and flabby, mitotic figures are present, and the appearance is that of an actively growing tissue. Such a condition is often termed a myosarcoma. It should

Fig. 64.—Leiomyoma; the tumor is more cellular than usual. × 300.

rather be called a malignant myoma, the term sarcoma being reserved for tumors of connective tissue origin.

RHABDOMYOMA

Tumors consisting of striated muscle are not only very rare, but they seldom occur in voluntary muscle. They are found in the heart, kidney,

testicle, and vagina. They are common in children, and probably arise from embryonic rudiments. As a rule they are malignant, but may occasionally be innocent.

EPITHELIAL TUMORS

Epithelium is a tissue which varies greatly in structure with its position in the body and the function it is destined to perform. It occurs in three main forms.

1. Squamous epithelium covering the skin, lips, mouth, tongue, pharynx, larynx, esophagus, vagina, and in a modified form the bladder.

2. Columnar epithelium lining the mucous membrane of the stomach, intestine, and uterus, and the tubular glands arising from that mucous membrane.

3. Epithelium, cubical or spheroidal in type, lining such acinous glands as the breast, pancreas, or prostate, or arranged in solid strands in organs like the liver.

In whatever form it occurs it presents certain common features: (1) the cells of which it is composed lie in apposition with one another, (2) they are arranged in groups, (3) the groups are separated by a fibrous stroma and (4) unlike the connective tissues the stroma does not intervene between the individual epithelial cells. Tumors arising from epithelium, however diverse in appearance, maintain these basal characteristics.

The innocent epithelial tumors reproduce the structure from which they originate; they are histioid in type. The malignant tumors may make no attempt to do so, or the attempt if made is never successful.

The innocent variety may assume two forms, the papilloma and the adenoma; the former arises from a surface, the latter from a gland.

PAPILLOMA

There are three varieties of papilloma which may conveniently be considered separately, depending on whether they arise from a squamous surface, from a mucous membrane, or from the wall of a cyst.

The *squamous papilloma* is commonest on the skin (Fig. 65), but may occur in the larynx and other parts covered with stratified epithelium. It consists of branched processes covered by proliferated squamous epithelium, or there may be only a single massive process. On the skin it forms a wart. With each advance of knowledge, however, it becomes apparent that many of these papillomata are not true tumors, but merely the result of some unrecognized irritant. The cutaneous warts of children, which often come out in crops and disappear after a varying interval, are certainly infectious in nature. The venereal warts (condylomata acuminatum) occurring in the region of the genital organs are of a similar character. Some so-called warts are in reality pigmented tumors, and probably not epithelial in nature.

The mucous *papilloma* grows from a mucous membrane, generally that of the bladder (Fig. 66) and rectum, but it may occur in any part of the alimentary canal. It is a soft villous tumor growing from a slender stalk, and in the bladder the process may be so numerous as to resemble seaweed. These tumors of the bladder are very liable to develop a malignant tendency. Many of them may be malignant from the beginning
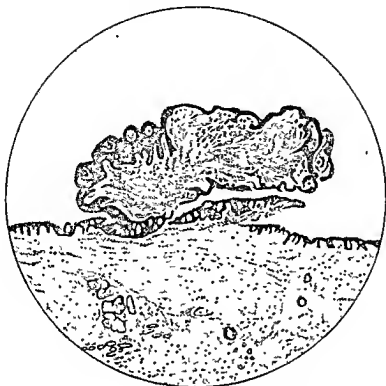
Fig. 65.—Squamous papilloma of skin.
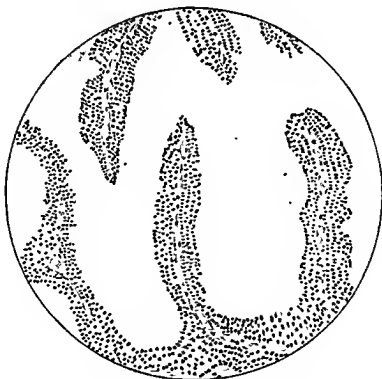
Fig. 66.—Mucous papilloma of bladder.

(see page 119). Infection with the Bilharzia may give rise to tumor-like masses in the bladder and rectum indistinguishable from a mucous papilloma, and these growths also may sometimes become malignant.

The *intracystic papilloma* may resemble a wart or a mucous papilloma. The former is seen in the interior of cysts of the breast (Fig. 67), the latter in the ovarian cystadenoma.
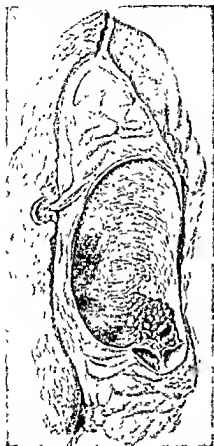
Fig 67.—Intracystic papilloma of breast.

ADENOMA

An adenoma is an innocent epithelial tumor of glandular origin. It varies in structure with the particular gland from which it arises In an acinous gland such as the breast or thyroid the cells surround acini in a perfectly regular manner, and may reproduce the glandular structure to perfection, even going so far as to produce the normal secretion of the organ. The lining cells are one or two layers in depth, but even when a number of layers are present this does not indicate malignancy. They rest upon a basement membrane formed of compressed connective tissue, and show no tendency to invade the surrounding tissue.

When the glandular secretion is abundant the acini of the tumor may become distended with fluid to form cysts, for they are not provided with ducts by means of which the secretion may escape. This is seen to best advantage in the ovary, where the acini are lined by tall columnar mucin-secreting cells, derived from a downgrowth of the superficial germinal epithelium, so that the tumor is called a cystadenoma, but it is also fairly common in the breast. The cells lining such cysts may atrophy from the pressure, becoming cubical or flattened, or they may proliferate and project as papillomata into the cyst spaces—a papillary cyst-adenoma.

Adenomata of the *breast* are of special importance on account of the difficulty sometimes experienced in distinguishing them clinically from carcinoma. They seldom occur as pure epithelial tumors, for there is usually a proliferation of fibrous tissue, more or less marked, the tumor being a fibro-adenoma. In many cases the fibrous overgrowth appears to be the dominant feature, that of the glandular tissue being secondary, so that the term adenofibroma would be more appropriate. The tumors present two varieties, one in which the fibrous tissue surrounds the

gland spaces, the other in which it projects into the spaces. These peri-canalicular and intracanalicular forms will be discussed more fully in the chapter dealing with diseases of the breast.

Adenomata of the *stomach* and *intestine* often project into the lumen, hanging by a slender stalk so as to form soft polypoid tumors which may give rise to intussusception.

In the *thyroid*, adenomata are very common, forming one variety of goitre. They may present the normal structure of the thyroid, except that the acini may be dilated and cystic, or they may be composed of small acini lined by large cuboidal cells and separated by an abundant stroma (Fig. 68).
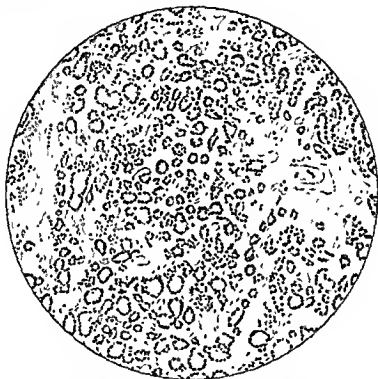
Fig. 68.—Adenoma of thyroid. The numerous small acini are separated by an abundant stroma.

Adenomata of solid glandular organs such as the *liver* and *adrenal* consist of strands of cells which it may be difficult to differentiate micro-scopically from the normal tissue. In such cases the diagnosis is most readily made from a naked-eye examination.

CARCINOMA

Carcinoma is the commonest variety of malignant disease. It occurs in all races of mankind and in many species of animals. In England and Wales one woman in eight and one man in eleven above the age of 35 years dies of cancer.

The most characteristic feature of carcinoma in the majority of cases is its peculiar hardness. Almost no other lesions are so hard. It is firmer than an adenoma or sarcoma because it contains more fibrous tissue

unless it is very rapidly growing and embryonal. Whereas a sarcoma is of uniform appearance, although perhaps with large areas of necrosis, carcinoma produces white streaks due to fibrosis and yellow spots due to focal fatty degeneration. Breast carcinoma, for instance, can nearly always be recognized with the naked eye from its appearance of a hard cicatricial nodule with chalky streaks of fatty epithelium.

A carcinoma is a tumor composed essentially of epithelial cells which tend to invade the lymph spaces of the surrounding connective tissue.

The *cells* are collected into groups separated by a stroma, which, however, does not penetrate between the individual cells of which the group is composed. In this respect a carcinoma differs fundamentally from a sarcoma, as epithelium differs from connective tissue.

Loss of Polarity.—Polarity is fundamentally direction of function. It is organization of a cell into two opposite poles, as in a magnet. This is best seen in an acinar gland, in which cell secretion moves in one direction, and is represented structurally by the position of the nucleus, Golgi apparatus, mitochondria and centrosome, as well as the relation of the cells to one another. In carcinoma there is a tendency to loss of polarity, particularly with respect to the mutual relationship of the cells. This is illustrated in adenocarcinoma, in the more anaplastic forms of which the loss of polarity may be complete, so that the loss may be taken as a measure of the degree of anaplasia.

The *stroma* varies greatly in amount and consistence, and plays an important part in determining the physical characters of the growth. It is called into existence by the stimulus of the epithelial cells, and, although secondary in character, it is nevertheless essential for the welfare of the neoplasm. If the thrombus which forms around an embolus of carcinoma cells impacted in a capillary does not become invaded by a stroma, the cells soon die and fail to form a tumor. A similar occurrence has already been described in connection with the experimental transplantation of tumors. On the other hand the connective tissue reaction may be so intense that the stroma chokes and kills the epithelial cells.

Extension.—A carcinoma generally grows along lymph spaces or vessels, and it may be possible to demonstrate the lymphatic endothelium around the cell mass. On looking at a microscopic section of a carcinoma it appears as if there were numbers of separate masses. It must be remembered, however, that the tumor forms one mass with branching extensions which are cut across in the section so as to give a fictitious appearance of multiplicity.

The nearest *lymph nodes* are involved by the process of permeation, cancer cells growing along the lymphatic vessel; or emboli may be carried by the lymph stream and lodge in the node. It is of great practical importance to remember that the nodes are not enlarged in the early stages, although they may be packed with carcinoma cells. On section the node is seen to contain a small white nodule, which later involves the whole node.

Metastases are set up in distant parts by the lymph or by the blood stream. The chief means of spread of carcinoma is the lymphatics, as that of sarcoma is the blood vessels, but a carcinoma may at any time invade a vessel and enter the blood stream. Sometimes there is wide-

spread permeation of the lymphatics by carcinoma cells, with the formation either of white lines or separate nodules. The latter lesion is illustrated in Fig. 69.

There are remarkable differences in the liability of different forms of cancer to produce metastases. Squamous-celled carcinoma involves the neighboring lymph nodes, but rarely the distant viscera. Carcinoma of the alimentary canal commonly involves the liver through the portal vein, but seldom more distant organs. The lungs are the common site

Fig. 69.—Metastatic carcinomatous nodules in pleura.

for metastases from carcinoma of other glands. In some cases of carcinoma of the prostate, thyroid, bronchus, and breast the metastases show an extraordinary preference for the osseous system, so that most of the bones of the skeleton may show deposits while the other organs may remain free. Tumors of the kidney (hypernephroma) may display a similar peculiarity.

Metastases reproduce, as a rule, the structure of the primary growth with remarkable fidelity, even to the extent of showing the same type of degeneration, as in the case of a colloid cancer. Occasionally, however,

there may be marked differences. A carcinoma of the breast with few cells and abundant stroma may appear in a lymph node as a highly cellular growth with scanty stroma.

Secondary Changes.—*Fatty degeneration and necrotic softening* are common, especially in the soft cellular forms. *Hemorrhage* may accompany the degeneration, but is not so common as in sarcoma. *Mucoid degeneration* may occur, especially in the alimentary canal and the breast, giving rise to the form known as colloid cancer. *Ulceration* is common in superficial cancers, as those of the skin, alimentary canal, uterus, and bladder. Ulceration is always accompanied by *septic infection*, and the condition of the patient usually takes a marked turn for the worse, with the development of cachexia, anemia, and other general symptoms of malignancy. If the infected area can be extirpated and cleansed there may be marked improvement in the clinical condition, even though removal of the whole tumor be impossible. In the serious consequences of secondary infection malignant disease bears a close resemblance to tuberculosis.

Classification.—Epithelium occurs in so many forms, and the divergencies from the normal in carcinoma are often so great, that to give a simple and at the same time satisfactory classification is a next to impossible task. For practical purposes, however, the carcinomata may be divided into two great groups.

1. *Squamous-celled carcinoma*, commonly called epidermoid carcinoma or epithelioma, arises from squamous stratified epithelium in the skin, esophagus, vagina, etc.

2. *Glandular Carcinoma.*—This may be an *adenocarcinoma* with an attempt, more or less successful, to reproduce gland spaces. The tumor cells may grow as small masses with abundant stroma (*scirrhous form*) or as large masses with scanty stroma (*medullary form*).

Mucoid cancer (colloid cancer, gelatinous cancer) is a term applied to a carcinoma the cells of which have undergone mucoid degeneration. It is not a separate form, and although commonest in the adenocarcinomata of the alimentary canal it may occur in a carcinoma simplex of the breast.

EPIDERMOID CARCINOMA: EPITHELIOMA

The term epithelioma is so well established and of such general usage that it is difficult to displace. It is obvious that all carcinomas are epitheliomas, that is to say epithelial tumors, but in practice the term has been confined to malignant tumors arising from squamous epithelium. Such tumors are better called epidermoid carcinomas.

Epidermoid carcinomas occur wherever squamous or transitional epithelium is found (Figs. 70 and 71), and as such epithelium differs depending on whether it occurs in the skin, the esophagus, or the bladder, so the epithelial growths in these regions present differences of structure. They all have certain features in common, however, by which they can be recognized.

The favorite site for an epidermoid carcinoma is a place where two different types of epithelium come together, such as the lip, the nostril, the eyelid, the upper end of the esophagus, the penis, or the vulva. In
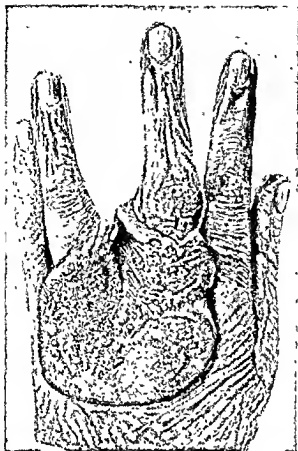
Fig. 70.—Epidermoid carcinoma of hand. Removed from an insane patient.

Fig. 71.—Epidermoid carcinoma of foot. The patient had been treated with Christian Science.

other positions it is usually associated with some form of chronic irritation, often developing at the edge of a chronic ulcer.

A typical epidermoid carcinoma, such as occurs on the lower lip, begins as a slight thickening or a small nodule. Ulceration usually occurs, the ulcer refuses to heal, and is covered with a crust. The edges of the ulcer present a characteristically raised rolled appearance, due to the new growth which is taking place. The lesion is markedly indurated. The nearest lymphatic glands become enlarged.

Microscopically solid columns of epithelial cells are seen growing down into the dermis, separated from one another by connective tissue (Fig. 72). These expand into bulbous masses which on section may appear quite detached. In course of time the cells nearest the center of these masses, being the oldest, undergo the same degenerative changes as are usual in normal surface epithelium, granules of eleidin appear in their cytoplasm, and finally the central cells become converted into a hyaline structureless mass of keratin, a process of keratinization or cornification. A mass is then formed in the center of which is a horny material, further out are granule-laden cells, and the periphery is formed by normal-looking squamous cells, often presenting the characteristic "prickle-cell" appearance, and arranged in a somewhat concentric manner (Fig. 73). These peculiar masses are known as "cell nests" or "epithelial pearls," but although highly characteristic of an epidermoid carcinoma they are often absent in rapidly growing tumors, and in the esophagus and bladder where cornification does not normally occur. The stroma is commonly infiltrated with inflammatory cells, lymphocytes, and plasma cells derived from the tissue, whose presence is due to the irritation produced by the epithelial masses. They probably represent a defense reaction on the part of the body.

Such are the features of a typical epidermoid carcinoma of the skin. Skin cancers are generally of relatively low malignancy. Metastases are late, and when they do occur they are usually confined to the regional lymph nodes. In the tongue and esophagus extensive ulceration is a marked feature, and cornification and cell nests are usually absent, but they may occasionally be found.

Carcinoma of the cervix uteri, one of the commonest and most dangerous of all forms of carcinoma, is of the epitheliomatous type, but differs from the typical epithelioma elsewhere. It is composed of thick irregular strands and masses of stratified cells showing numerous mitotic figures, but there are no cell nests nor cornification. The stroma is plentifully infiltrated with plasma cells.

In organs lined by transitional epithelium such as the bladder the epidermoid carcinoma consists of irregular masses of transitional cells, but there are no prickle cells nor cell nests. Cornification is absent.

A pitfall for the pathologist is the fact that in blastomycosis of the skin there may be an epithelial invasion of the deeper structures which may so resemble epidermoid carcinoma as to deceive the very elect.

An epidermoid carcinoma may occasionally originate in an organ lined by columnar epithelium. This is an example of metaplasia; for instance in the gall bladder, where the occurrence is commonest, the columnar epithelium reverts to the squamous type, often as the result of irritation

Fig. 72.—Epidermoid carcinoma of skin of low grade; keratinization is well marked

Fig. 73.—Epidermoid carcinoma showing a typical epithelial pearl. × 125.

from calculi, and an epidermoid carcinoma develops upon this debased epithelium.

Rodent Ulcer.—There is one form of squamous-celled carcinoma of the skin which differs in important particulars, both clinical and histological, from the ordinary epidermoid carcinoma. It usually occurs on the upper part of the face, about the cheek, nose, eyelid (Fig. 74) or ear, but *not* at the junction of skin and mucous membrane, and although it may eventually produce the most terrible destruction and disfigurement through its eroding action (Fig. 75) it grows very slowly, often over a course of many years, the glands are not involved, and metastases are not set up. The tumor is frequently multiple, and the multiple growths may be confined to one area or may occur in different areas. It is called rodent ulcer, or by some basal-celled carcinoma, under the belief that it
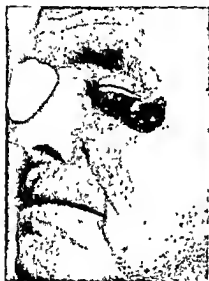
Fig. 74.—Rodent ulcer, comparatively early stage.

Fig. 75.—Rodent ulcer with complete destruction of the contents of the orbit.

originates from the basal layer of the epidermis. It is better to use the term basal-celled to indicate that the cells of the tumor resemble those of the basal layer. Some of the tumors may arise from this basal layer, others from hair follicles, and still others from misplaced cell groups from the epidermis thus explaining their frequent occurrence along the line of embryonal fissures. The fact that they are usually confined to the face suggests that the irritation of sunlight may be an important etiological factor. Molesworth's observations on rodent ulcer in Australia support this view. Rodent ulcer is extraordinarily prevalent in that country and is practically confined to white people of the laboring class, whose skin is unprotected against the very bright sunlight of high actinic value. It is seldom seen in the dark-skinned Italians, many of whom work on the farms.

The *microscopic appearance* is that of solid masses or columns of cells

growing downwards into the dermis (Fig. 76). The columns all reach to about the same level, have a characteristically club-shaped appearance, and the connection with the epidermis can rarely be seen in a given section. The cells are small and compact, with scanty protoplasm and a darkly staining nucleus, and are very different in appearance from the pale inflated cells of an epithelioma. There are no prickle cells, cell nests, nor cornification. The layer of cells on the outside of the mass is frequently columnar in shape.

Adenoid Cystic Epithelioma.—This relatively uncommon form of epidermoid carcinoma, *also called Brooke's tumor*, is of low grade malignancy. The cells may be of the squamous or basal-cell type, and show an irregular glandular arrangement, often with the formation of small cysts; hence the name adenoid cystic epithelioma (Fig. 77). The tumor may project like a horn from the surface, and seldom infiltrates deeply.

Fig. 76.—Rodent ulcer. The dark cells and club-shaped processes are characteristic of basal-cell carcinoma. × 33.

Tumors of Sweat Glands.—These tumors resemble the adenoid cystic epithelioma The benign form, known as a *spiradenoma* (*speira*, a coil), is often multiple. A common position for these tumors is the scalp, where they may form what is known as a "turban tumor." Microscopically the lesion consists of large numbers of sharply circumscribed masses of cuboidal cells (Fig. 78). The ducts may be dilated to form cysts. *Adenocarcinoma* is much less common, and is of low malignancy.

Fig. 77.—Adenoid cystic epithelioma. × 14.
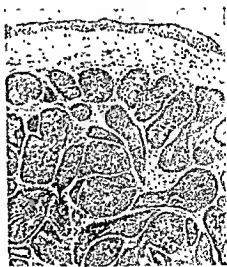
Fig. 78.—Spiradenoma. × 67.

ADENOCARCINOMA

A columnar-celled carcinoma may arise either from mucous membranes or from glands lined by columnar epithelium. It occurs especially in the

stomach, large intestine (cecum and rectum), gall bladder, pancreas, uterus, and prostate.

The tumor may conveniently be studied in such an organ as the stomach or intestine. Two main forms occur, the nodular which projects as an ulcerated mass, often polypoid in form, into the stomach, and the sessile which infiltrates the walls and produces a localized thickening. The former presents the more characteristic appearance. The nature of the mucosa changes at the edge of the growth with dramatic suddenness. The glands become highly irregular, with numerous branching processes, and may be filled with epithelial cells. The cells stain more darkly than those of the normal mucosa, frequently show mitosis, and are no longer limited by a smooth basement membrane, but wander out into the surrounding stroma. Most characteristic of all, glands are found where they should never
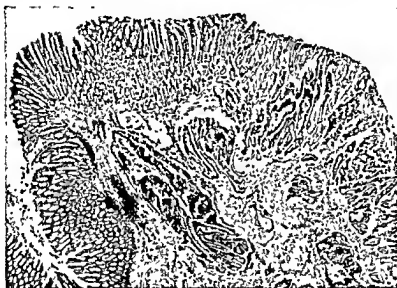
Fig. 79.—Adenocarcinoma of colon, showing sudden change in type of mucosa and invasion of submucosa. × 10.

normally occur, namely deep to the muscularis mucosae (Fig. 79). The stroma is densely infiltrated with inflammatory cells.

In the sessile variety the glandular arrangement may be lost, the stroma may be so dense as to be scirrhous in type, and the cells may be arranged as solid strands, so that the growth has become a carcinoma simplex. Such growths of the stomach illustrate very well the essential similarity between the two types of glandular cancer, the adenocarcinoma and the carcinoma simplex.

Metastases are very common in the neighboring mesenteric glands, in distant glands, especially the supra-clavicular group, and in the liver.

Mucoid degeneration is of not infrequent occurrence in the stomach and large intestine and also in the breast and bronchus (Fig. 80). Large masses of gelatinous new growth are found rather like sago pudding, with

great thickening of the stomach wall. The metastases have the same mucoid appearance as the parent growth. Two varieties may be distinguished: (1) a primary form arising as a tumor of mucus-secreting cells, and (2) a secondary form which is merely a mucoid degeneration of a pre-existing adenocarcinoma. The primary form constitutes only 15 per cent of all the cases, shows a high mortality, and presents no glandular arrangement. In the secondary form the glandular arrangement is present in part, and the degree of malignancy is considerably lower.

Scirrhous Carcinoma.—Malignant glandular epithelium may fail to form gland spaces, but may grow in solid masses and cords. This is likely to occur in the case of the cuboidal epithelium of such glands as the breast. If the cells are scanty and the stroma dense and abundant the tumor is spoken of as scirrhous in type. The cells are arranged in small groups and columns, or they may be in single file growing along lymph spaces (Fig. 81). Mitotic figures are not common. Owing to the desmoplastic (stroma-producing) nature of the growth the lesion is densely hard.

Medullary Carcinoma.—This is similar in cellular arrangement to the scirrhous form, except that the cell masses are large and the stroma scanty. The cells are large and spherical, and mitoses are numerous. The tumor is soft

Fig. 80.—Mucoid cancer of stomach. The submucosa is invaded by carcinoma cells which have undergone an extreme degree of mucoid degeneration.

compared with the scirrhous form, so that it is also called encephaloid or brain-like. The types are often combined, and the distinction between the two is not a vital one, except that the medullary form may be expected to be more radiosensitive than the scirrhous form.

Adeno-acanthoma.—In 1907 Herxheimer called attention to a form of carcinoma in which there is an intermingling of squamous-cell carcinoma and adenocarcinoma (Fig. 82). A number of such tumors have been reported in the stomach, uterus, breast, gall bladder, pancreas, large bowel, and lung. The condition is now called adeno-acanthoma, and appears to be a manifestation of the capacity of glandular cells to take on squamous cell characteristics. The intermingling of cell types is well seen in the illustrations of Herxheimer's original exhaustive paper and in those of Pasternack's more recent article.

Fig. 81.—Scirrhous carcinoma; cancer cells in lymph spaces. × 240.

Fig. 82.—Adeno-acanthoma of bronchus. × 240.

NERVOUS TISSUE TUMORS

The nervous system is developed from epithelial cells which line the neural canal, and from these cells both the nerve cells and the neuroglia are formed. Thus the neuroglia, although resembling connective tissue in structure and function, is epithelial in origin. During development large numbers of cells migrate to form the sympathetic nervous system, and many of these penetrate the medulla of the adrenal, so that tumors composed of nerve cells may arise in that organ. As might be expected, two varieties of tumor may be met with in the nervous system and its derivatives, the glioma, a common tumor arising from the neuroglia, and the neuroblastoma, a rare tumor arising from primitive nerve cells or neuroblasts.

The *glioma* is a tumor of the central nervous system, varying greatly in microscopic structure and in degree of malignancy. These tumors are described in connection with diseases of the nervous system (page 629).

The *neuroblastoma* is a tumor of sympathetic nerve cells and fibers. Its usual site of origin is the adrenal medulla, but it may occur in the abdominal or thoracic sympathetic system. The neuroblastoma is discussed in connection with diseases of the adrenal gland (page 406).

Tumors of the nerves, both peripheral and cranial, are considered in connection with diseases of nerves (page 661).

ENDOTHELIOMA

The endotheliomas form a very ill-defined group of tumors, and it is difficult to decide what should be included. The so-called endothelioma of the dura mater is now regarded as a fibroblastoma (fibroma), and

other growths such as the parotid tumor have been rescued from the group. The tumor which Ewing has called an endothelial myeloma is considered in connection with the diseases of bone. Endothelium is a structure which lines cavities, and the endotheliomas show this lining tendency, but the cells may also proliferate to form solid masses. The endothelial tumors regarding which there can be no difference of opinion are those which arise from blood and lymph vessels, the hemangioma or hemangio-endothelioma, and lymphangioma or lymphangio-endothelioma. The hemangioma is commonly called an angioma.

Angioma.—An angioma (hemangioma) is a tumor consisting of new-formed blood vessels. Frequently, however, it is difficult to say if a collection of vessels is a true neoplasm or merely a dilatation of previously
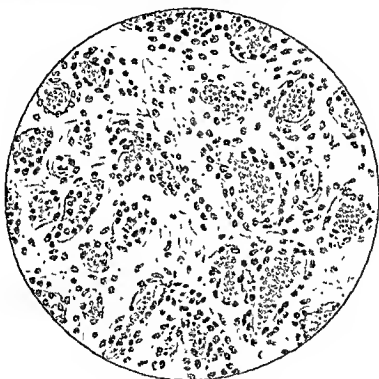
Fig. 83.—Capillary angioma.

existing vessels (telangiectasis). Two forms of hemangioma are recognized, the capillary and the cavernous.

Capillary Angioma.—This consists of a network of capillaries filled with blood (Fig. 83). The lining cells, which are large and swollen, may be several layers in depth, and the lumen may be very small, sometimes containing no blood. The cells may proliferate to such an extent that they obliterate the lumen, and the tumor then resembles an endothelioma. The cells may be arranged in whorls, especially around the blood vessels. It is known that the first stage in the formation of vascular spaces from the mass of proliferating cells is the development within each cell of a vacuole, which gradually enlarges until the entire cell becomes flattened. In many of the cells the wall gives way so that the vacuoles

coalesce, and new blood spaces are thus formed, at first irregular in shape, but later conforming to the regular form of capillaries.

The common site is the skin, but it may occur in the mucous membrane of the nose, lip, tongue, gum, or rectum, in which latter position it may occasion severe hemorrhage.

A cutaneous angioma is usually a bright red, sharply defined patch, not raised above the general level, but it may present a somewhat velvety surface. It is generally present at birth, and from a minute red spot it may spread to cover a large surface. The favorite position is the face or head, where it often follows the distribution of the fifth nerve, and it is almost always strictly unilateral, stopping short at the middle line.
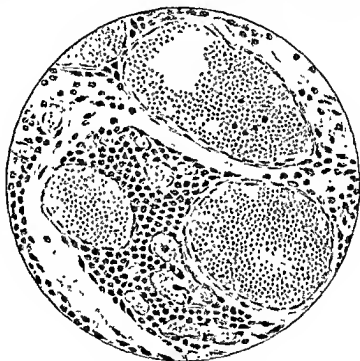
Fig. 84.—Cavernous angioma.

These angiomas are commonly known as port-wine stains, birth marks, or strawberry marks. In England the term nevus is used, but this should be confined to an entirely different form of neoplasm also occurring in the skin (see below).

Cavernous Angioma.—The structure of this tumor is that of erectile tissue. It resembles a fine sponge, and on section is of a deep red color. It consists of large blood spaces or sinuses lined with endothelium (Fig. 84). The common site is the liver, where it may be multiple (Fig. 85). It is also found in the skin in various regions, including the lip, where it forms a raised mass, often of distinctly higher temperature than the surrounding structures, the overlying skin generally shows a bluish tinge, and gentle pressure may succeed in emptying the tumor. It may infiltrate the subcutaneous tissue and underlying muscles, and I have seen the

most alarming hemorrhage result from an ill-advised attempt at removal in such a case.

Lymphangioma.—A tumor composed of lymphatics is much less common than a hemangioma. It is usually localized, but may be diffuse. The diffuse form may occur in the tongue giving rise to macroglossia, or in the lip giving macrocheilia. The localized form may be a capillary, but more usually a cavernous lymphangioma. It occurs most frequently in the skin and subcutaneous tissues, forming a doughy swelling which may be mistaken for a cold abscess. In the neck it may form a cystic mass, known clinically as a *cystic hygroma*. This and the other forms of lymphangi-
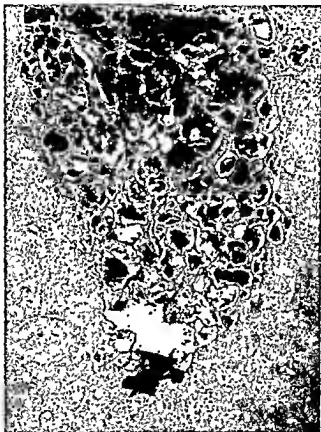
Fig. 85.—Cavernous angioma of liver. × 10.

oma are more common in children. Microscopically the picture is the same as a hemangioma, except that the endothelial-lined spaces are filled with clear lymph and a few lymphocytes instead of blood.

The cystic hygroma grows from the lymph sacs in the neck. These develop as solid buds, which later become connected with the internal jugular vein. In certain cases this connection is not established, and the sacs give rise to hygromas. The lining cells of the hygroma probably produce the lymph which fills the cysts.

Glomangioma.—This lesion is commonly called glomus tumor, and in the past it has masqueraded under a variety of names of which the chief is subcutaneous painful tubercle. It has the appearance of an angioma

with the symptoms of a neuroma. Its true character was recognized for the first time in 1924 by Pierre Masson.

The glomus (Fig. 86A) is a specialized arteriovenous anastomosis surrounded by large pale cells (glomus cells) between which are numerous firm medullated and nonmedullated nerves. It is most abundantly present in the region of the nailbed, the tips of the fingers and toes, and the palmar surface of the phalanges. The tumor which springs from it is therefore commonest in these sites, but it may occur anywhere on the upper and lower limbs, although not on the trunk. The function of the glomus is supposed to be concerned with heat regulation, the large vascular channels of which it is composed being under the influence of the abundant nerve supply.

The glomangioma, a perfectly benign and circumscribed tumor, blue or reddish in color, and seldom exceeding 1 cm. in diameter, is merely an
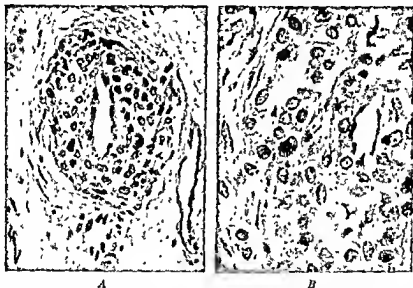
Fig. 86.—A, Normal glomus. B, Glomangioma The similarity in the type of cells and in their perivascular arrangement is evident. × 480.

enlarged glomus (Fig. 86B). It consists of tortuous vascular channels in the walls of which the plain muscle has been replaced by large pale cells of the epithelioid type with clear or vacuolated cytoplasm. The cells may be clumped in large masses without a definite lumen. Sometimes plain muscle fibers intervene between the lumen and the mantle of epithelioid cells. These cells, indeed, are supposed to represent altered muscle fibers. Abundant nerve endings are seen between the epithelioid cells, and it is pressure on these endings which is responsible for the pain that is so characteristic a symptom. In a considerable number of cases the appearance of the tumor is preceded by a single severe trauma.

The clinical symptoms are highly characteristic and remarkably severe for so small a lesion. At first there are attacks of pain limited to a small area, although no lesion may be visible. Gradually the attacks become more severe, and are stabbing or burning in character. The pain, which

may be radiating and neuralgic in character, may be spontaneous or may be caused by the slightest pressure. It is probably caused by the dilated glomus vessels pressing on the numerous nerve endings. Removal of the tumor is followed by complete and permanent relief. No minor operation wins a greater share of the patient's gratitude.

THE MELANOMATA

The melanomata or pigmented tumors form a class by themselves, entirely separate from any other tumors and presenting many problems of remarkable interest regarding their origin, their character, and their mode of spread. There are two forms of pigmented tumor, the one innocent, the other malignant. The former is known as a benign melanoma or a pigmented nevus, the latter as a malignant melanoma or a melanotic sarcoma. In actual practice it is common to refer to the innocent tumor as a nevus, and to the malignant tumor as a melanoma.

The *origin* of the tumor cells has for long been a matter of hot dispute, nor indeed has the question even yet been decided. The research of Masson has thrown new light on the origin of the melanomata. He has
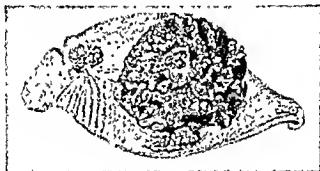
Fig. 87.—Pigmented nevus.

shown by means of special staining methods that between the cells of a nevus there is an abundance of fine non-medullated nerve fibrils. The sensory nerves of the skin end in special sense organs. In the dermis the medullated nerve fibers terminate in Meissner's corpuscles, from which non-medullated fibers pass into the epidermis and end in the tactile corpuscles of Merkel-Ranvier. Both of these corpuscles are composed of specialized cells. Associated with these cells there are pigmented chromatophores, known as the cells of Langerhans. According to Masson a melanoma is merely a proliferation of the entire end organ, which in the dermis is represented by Meissner's corpuscles plus chromatophores and in the epidermis by the corpuscles of Merkel-Ranvier plus chromatophores. This would bring a nevus into line with the pigmented spots found in the skin in neurofibromatosis, and would serve to harmonize both the epithelial and the chromatophore theories of origin.

Nevus.—The nevus or mole may be pigmented or non-pigmented; the former is common, the latter rare. The average person has at least 20 pigmented moles in various parts of the skin. The pigmented mole may be almost level with the surface, or may be markedly raised (Fig. 87). It

may be grey, brown, or black in color. The surface is often covered with coarse hairs. Whilst it may be found in any part of the body it usually occurs on the face, the neck, or the back. Those moles situated on exposed parts are most liable to malignant change, but even on covered parts of the body, as the back or the foot, they may be subject to irritation, and such moles are always a source of danger. The condition must be regarded as a congenital one, but the mole may not be apparent at birth, only becoming evident later in childhood.

The great majority of moles fortunately pursue an absolutely innocent course, growing slowly for a long period, then becoming quiescent, and finally undergoing retrogressive and fibrotic changes. As the result of irritation, however, or of injudicious and incomplete surgical interference, they may at any time develop malignant characteristics.

Microscopically we may distinguish the congenital mole of infants and children and the mole occurring in adults. In the *infantile* form the

Fig. 88.—Nevus of skin, showing masses of nevus cells in papillae of corium.

cells of the deeper layers of the epidermis or those of the hair follicles and sweat glands become swollen, their cytoplasm clear, and their nuclei hyperchromatic. The cells become isolated and form clumps in the underlying tissue. Numerous pigment granules frequently are found in these cells. As the cells become isolated from the epidermis they gradually lose their pigment and enter upon a period of quiescence. The sequence, therefore, is proliferation with pigmentation, depigmentation, and quiescence. In the *adult* form the epidermis is seen to send elongated processes down into the corium, and in the intervening papillae there are alveolar groups of clear cells with dark nuclei (Fig. 88). Some of these nevus cells may be colorless, whilst others are deeply pigmented. As a rule no connection with the epidermis can be seen, and the picture is one of quiescence, but occasionally the process of derivation from the epidermis may apparently still be going on.

Malignant Melanoma.—This tumor is often known as a melanoma or a melanotic sarcoma. The great majority of the tumors arise from a pre-

existing pigmented mole, usually one which has been subjected to chronic irritation. There are, however, two regions, the sole of the foot and the external genitalia, in which moles are rare whereas melanomas are common, so that it is possible that in these areas the melanoma is not preceded by a mole. It is of prime importance to recognize the signs indicating that a mole is changing into a melanoma. These are a sudden increase in size and vascularity, darkening in color, superficial ulceration and bleeding. Brown moles can usually be left alone; it is the black ones which hold the possibility of danger. When a mole is on a site exposed to irritation (face, shoulder, etc.) it should be regarded with suspicion. The

primary growth may be in any region of the body, but the face, the back, and the foot are specially common sites. The tumor may begin in the nail fold of the toe and occasionally of the finger (melanotic whitlow). Metastatic nodules in the skin are often the first to attract clinical attention (Fig. 89), and when the presence of these cutaneous nodules suggests the possibility of melanoma, as it should do, a primary lesion in the shape of a pigmented mole must be carefully looked for.

Should it not be found, the eye must be examined, because this is an occasional site of the primary lesion. Both pigmented moles and malignant melanomas are found in the choroid and in the ciliary body. This has been taken as an argument in favor of the mesoblastic origin of these tumors, but it is highly probable that many of the pigment cells of the choroid arise in the retina and migrate into the choroid. The study of pigment behavior in the lower animals such as the amphibia makes movement of

Fig. 89.—Melanotic growths of skin in various stages of development. The primary growth was in the heel.

the pigment-containing cells easy to understand. The ocular tumors may therefore also be regarded as epithelial in origin.

It may be that no primary tumor is found either in the skin or in the eye. The metastases may still be those of melanomata for occasionally the primary lesion may be in internal organs such as the adrenal, the bowel, and the meninges. Melanoma of the rectum sometimes occurs, although not nearly so often in man as in the horse. It really arises in the anal canal, spreading upwards into the rectum and bulging into the lumen. The cerebral tumors arise from the pigmented cells of the pia. Finally there is an obscure group of cases where no primary tumor can be found either clinically or at autopsy.

Structure.—There are few tumors which may present a more varied

microscopic picture than does the malignant melanoma. Usually the
picture is characteristic enough and the diagnosis is easily made. The
cells are large, polyhedral, and epithelial in type. The cytoplasm is pale
and the nucleus large and vesicular. As a rule there is a distinct alveolar
grouping of the cells, the groups being separated by a stroma which is
usually scanty but may be quite abundant (Fig. 90). Such an arrange-
ment is strongly suggestive of an epithelial tumor. In other cases the cells
are arranged quite diffusely. Again the cells may be elongated and spindle-
shaped, so as to give a picture of fibrosarcoma. One part of the section
may show a carcinomatous appearance, another part a sarcomatous one
(Fig. 91). It is not too much to say that a melanoma may simulate a
carcinoma, a sarcoma, an endothelioma, and even a lymphosarcoma.
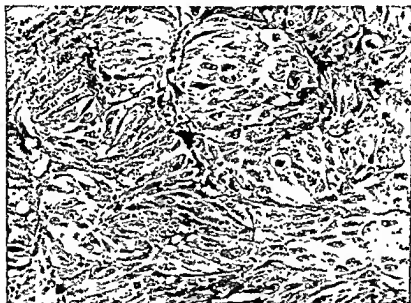
Fig. 90.—Malignant melanoma in skin showing characteristic acinar grouping of the
cells, but no pigment. × 275.

In the eye the tumor cells are usually of the spindle type, but they may
present an epithelial form and arrangement.

The microscopic evidence of the malignant transformation of a nevus
is usually readily recognized but sometimes presents great difficulty.
The tumor cells are no longer confined to the usual site, but are evidently
spreading to the deeper tissues. There is an increased vascularity, the cells
have become larger, the nuclei are hyperchromatic, and mitotic figures
can be seen. Pigmentation is usually marked, but this cannot be regarded
as an invariable criterion. In one part of a section the cells may be loaded
with yellow pigment, whilst in another part all the cells may be pigment
free. The character of the pigment also varies. It is usually in the form
of very fine yellow granules scattered like dust throughout the cytoplasm
(Fig. 92). In an adjoining field the cells may be filled with coarse yellow
lumps varying greatly in size.

Spread.—The *metastases* are the most important feature of a melanoma. The primary growth seldom attains a great size, nor does it occa-
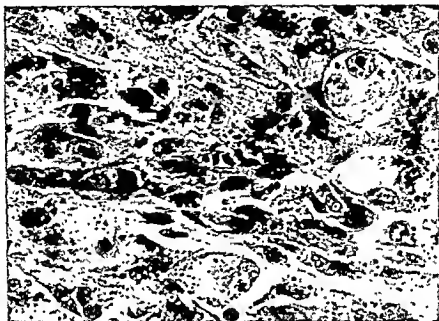
Fig. 91.—Malignant melanoma showing a very varied cell picture, partly suggesting sarcoma and partly carcinoma. × 500.
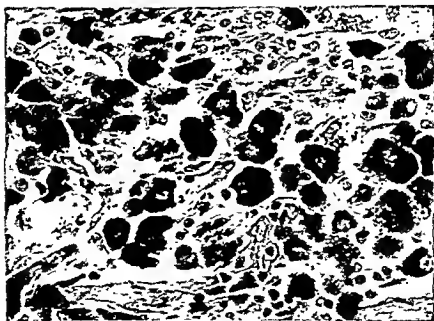
Fig. 92.—Malignant melanoma of the eye; many large cells loaded with pigment. × 450.

sion any serious clinical disturbance. It is the widespread metastases which constitute the lethal factor. These frequently first appear in the skin, where they form numerous small firm nodules which may or may

not be pigmented. The spread may be either by the blood or the lymph stream. As the result of blood infection there may be numerous secondary growths in the lungs, liver, kidney, brain, and many other organs.

Even after the tumor has become definitely malignant, as shown by enlargement and an increase of pigmentation, the subsequent history may vary greatly. In many cases the spread is chiefly by the lymph stream, with involvement of the regional lymph nodes. Soon after a mole becomes malignant the tumor cells pass via the lymphatic vessels to the regional nodes, but further growth in the nodes may be delayed for months or even for years. Sampson Handley, in his Hunterian lecture on melanomata, has emphasized the importance of removal not only of the neighboring glands but of the intervening lymphatics which are also implicated. Thorough treatment of such a nature at this stage of the disease may result in a complete cure. Occasionally the disease, although malignant, may remain localized for a number of years, only to become generalized in the end. Melanomas of the eye spread by the blood stream, not by the lymphatics. It may be many years, however, long after the eye has been removed, that metastases first become apparent. The secondary growths are often in the liver.

Melanemia and melanuria are both occasional occurrences. The serous membranes and the lining of the blood vessels may become pigmented.

HYPERNEPHROMA

There has been much difference of opinion as to the origin of this renal tumor. For long it was believed to arise from "rests" of adrenal cortical tissue embedded in the kidney. It is now certain that most if not all of these tumors are of renal origin; they are carcinomas of the kidney, although their high lipoid content is suggestive of adrenal structure. They are considered on page 399.

CHORIONEPITHELIOMA

The chorionepithelioma is a tumor in a class entirely by itself, for it originates from the cells of another individual, the cells of the chorionic villi of the fetus.

Chorionepithelioma of the uterus is always connected with pregnancy, but it is usually preceded by abortion, and in a considerable proportion of cases by the development of a hydatid mole. Only rarely does it occur in connection with a normal pregnancy, and then more commonly after than during the period. The invasive character of the chorionic epithelium for some reason continues unchecked, and a malignant tumor is the result.

A soft, ragged, fleshy mass develops in the uterus, usually in the fundus. It is extremely hemorrhagic, and consists mainly of blood clot. It can be seen invading the uterine wall.

The further gross and microscopic characteristics, together with the peculiar clinical behavior of the tumor, are considered in Chapter XXIII.

TERATOMATA

A teratoma is a tumor consisting of different tissues or organs derived from more than one primitive germ layer. It may be regarded as an

attempted formation of a new individual within the tissues of the patient. The tumors vary from simple cystic structures to complex monsters.

It seems probable that a teratoma may arise either from a segregated ovum or a segregated blastomere. From the segregated ovum a complete individual could theoretically be developed by parthenogenetic division. This is the best explanation of the rare chorionepithelioma of the testicle, which may be regarded as an imperfect fetus that has formed fetal membranes with the invasive power characteristic of the ordinary chorionepithelioma following pregnancy. A segregated blastomere is the probable origin of most of the solid teratomas of the ovary and testicle, the dermoid cyst of the ovary, and the teratomas arising in the roof end of the mouth and at the lower end of the sacrum. These tumors are a jumble of tissues, e. g., skin, hair, brain, cartilage, muscle, teeth, etc. In these cases the blastomere may be regarded as totipotent. In the teratoma of the kidney (Wilms' tumor) the blastomere seems no longer to be totipotent, so that the constitution of the tumor is much simpler.

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CHAPTER IX

CYSTS

A cyst is a collection of fluid in a rounded cavity surrounded by a definite wall or sac. Such localized collections of fluid are very common in the body. They form so heterogeneous a collection that it is difficult to combine them all under one common head, nor indeed is much to be gained by doing so. Moreover it is difficult in some cases to determine what should or should not be called a cyst.

Many cysts will be considered in detail when the organs in which they occur are discussed. Some of the more striking examples may be briefly considered in this place. We may divide cysts into the following groups.

1. Retention cysts.
2. Cysts of new formation; blood cysts.
3. Cysts of developmental origin.
4. Parasitic cysts.

RETENTION CYSTS

The blockage of the duct of a gland may be followed by cystic distension due to accumulation of the retained products. Such cysts are common in the breast and kidney, but the two important examples are the sebaceous cysts and the mucous cysts. Even in glands which have, no external duct there may be cystic dilatation from excessive secretion on the part of the lining epithelial cells, as in the case of the thyroid.

Sebaceous Cysts.—A sebaceous cyst forms as the result of obstruction to the duct of a sebaceous gland either from dirt or inflammation. It is lined by several layers of flattened epithelium, these representing the secreting cells of the gland. The cyst contains a soft porridge-like material which consists of desquamated keratin and contains fat and cholesterol crystals. Epidermoid carcinoma may develop in about 5 per cent of cases.

These cysts are commonest on the scalp and face, where they are frequently multiple, and although usually small they may attain the size of an orange. They also occur on the neck, shoulders, and back. The cyst forms a soft, doughy, globular swelling on the middle of which there may be a small black speck representing the closed duct. On the scalp the covering hair is often greatly thinned through pressure. As the cyst is situated in the substance of the skin the latter cannot be moved over it, thus contrasting with the dermoid cyst presently to be described.

The cyst may become inflamed and suppurate, or the overlying skin may ulcerate, giving rise to a condition which may closely resemble a malignant ulcer.

Mucous Cysts.—A mucous cyst has an origin similar to that of a sebaceous cyst, from obstruction to the duct of a gland in a mucous membrane. Not nearly so common as the sebaceous cyst, it appears as a small, tense,

bluish mass, seldom attaining to any size, and containing clear mucinous fluid.

The commoner sites are the mucous surfaces of the lips, cheeks, tongue, and vulva. In the floor of the mouth under the tongue a mucous cyst constitutes the principal variety of *ranula*, which is a cyst of the sublingual gland, although occasionally the gland involved may be the submaxillary. It can be readily recognized from its bluish and somewhat translucent appearance.

CYSTS OF NEW FORMATION

Exudation of fluid from the blood vessels or lymphatics into a pre-existing cavity such as a bursa must not be regarded as a cyst. Similarly effusions of blood into a tumor or into a soft organ such as the brain are not to be included in this category. When, however, there is the formation of a new cyst wall about the fluid as well as an exudation of new fluid, the resulting condition may be called a true cyst.

Blood Cysts.—Of these exudation cysts the most important are the blood cysts. A hematoma in the subcutaneous tissues or a cerebral hemorrhage may, instead of being absorbed, undergo liquefaction and become surrounded by a very definite wall of fibrous tissue. Hematoidin crystals are present in the inner layers of the cyst wall, and the contents are a clear yellow fluid.

What are often called *blood cysts of bone* are not true cysts, but extravasations of blood into a giant cell tumor or sarcoma, with consequent destruction of the tumor substance. There is no cyst wall.

Serous Cysts.—These cysts may commence as collections of fluid in the lymphatic spaces of the connective tissue in response to pressure, thus forming retro-mammary bursae. A rare variety occurs in the mesentery, and may contain either serous or chylous fluid.

CYSTS OF DEVELOPMENTAL ORIGIN

The most important of these is the dermoid cyst, but the dentigerous cyst may also be mentioned; although it is not a true cyst, the condition known as cystic hygroma will be considered in this connection.

Dermoid Cysts.—The dermoid cyst of the ovary will be considered later in connection with diseases of that organ. It is an entirely different condition from that under discussion, represents an attempt at the formation of a new individual, arises as a result of the abnormal development of an ovum, and to avoid confusion might well be called a dermoid tumor. Both conditions are called dermoid because of the skin and its derivatives which form so prominent a feature in the cyst wall.

Dermoid cysts are often termed *sequestration dermoids*, because they are formed by the inclusion of a rudiment of skin during the closure of one of the various embryonic clefts and fissures. They may arise from a vestigial epithelial-lined structure.

The cysts consist of a fibrous wall formed of cutis vera lined by stratified epidermis showing the normal papillary arrangement and containing hair follicles, sweat glands, and sebaceous glands. They contain sebaceous matter produced by the glands in the cyst wall as well as hair. They are always congenital, but may increase in size during childhood, owing to

continued secretion of the sebaceous contents. As the cyst is situated beneath the deep fascia the skin is freely movable over it.

The common position for dermoids is the angles of the orbit, especially the outer, and the upper eyelid. Occasionally they may occur in the scalp (Fig. 93), the external ear, or the tongue. When overlying the skull the bone under the cyst is often defective, and the cyst may be connected with the dura mater by a pedicle. In the neck they may be in the middle line or situated laterally. The latter are called *branchial cysts*, since they arise from imperfect closure of a branchial cleft. The cyst may originate from the second cleft, in which case it is below and a little behind the angle of the jaw, or from the third cleft when it is on a level with the hyoid bone.

An *implantation dermoid* is a cystic lesion of the hand and fingers lined by squamous epithelium, and supposed to be due to portions of epidermis being carried into the deeper tissues by a punctured wound. It is confined to those whose occupation exposes their hands to trauma, *e. g.*, laborers, carpenters, gardeners, etc. King points out that the common belief regarding the etiology of these cysts is probably wrong. The trauma need not be penetrating and is often merely a jarring. There is a latent period between the trauma and the development of the cyst, which varies from a few months to several years. The wall of the cyst consists of fibrous tissue lined by squamous epithelium, and the contents are a white greasy material full of cholesterol crystals. King suggests that the cyst is formed not from epithelium carried in from the surface but from the epithelium of sweat glands. A hematoma follows the injury and a cyst is formed. The irritation of the cyst contents stim-

Fig. 93.—Dermoid cyst containing hair.

ulates the epithelium of the sweat glands to proliferate. These cells are at first columnar, but later become squamous. Post-traumatic epidermoid cysts is a preferable term to that of implantation cysts.

Cysts and Tumors of Dental Origin.—The tooth is a complex structure, partly ectodermal, partly mesodermal in origin, and a variety of cysts and tumors may arise from it. These lesions partake of the character both of cysts and neoplasms; the tumors are cystic, and the cysts are neoplastic.

Each tooth is developed from a dental papilla, which consists of a mesodermal projection covered by an epithelial cap derived from surface epithelium and known as the *enamel organ*. The deeper layers of cells in the enamel organ is columnar in type and is called *enameloblasts*, for it is they which produce the enamel. The *dental* sac is the fibrous membrane which surrounds the developing tooth. The tooth follicle is the unit composed of mesodermal papilla, enamel organ and dental sac. It is

evident that a variety of tumors and cysts may arise from so complex a structure. The starting point in many cases is probably the groups of cells derived from the enamel organ or from the epithelium from which it originates, groups which Malassez has shown to be scattered along the course of the tooth even in adult life, and which have been called paradental epithelial débris. These epithelial rests are situated in the substance of the bone, and the cysts and tumors of dental origin occur in the same situation.

Bearing these developmental details in mind it is possible, as Stout points out, to simplify the complex nomenclature with which the literature is filled, and to recognize three main types of lesion: (1) *paradental*

Fig. 94.—Adamantinoma, showing the gland-like appearance produced by degeneration of the center of the masses.

epithelial cyst, a cystic lesion arising from paradental epithelial rests, (3) *adamantinoma,* a tumor arising from the remnants of the enamel organ or the paradental rests, and (3) *odontoma,* a composite tumor arising from disordered growth of the whole tooth germ.

Paradental Epithelial Cyst.—This may also be called a dentigerous cyst, although in the past this term has been used in a more restricted sense. The cyst may occur at any age, but is commonest in middle life. It usually remains small, being discovered by chance in a roentgenogram, but it may expand the jaw and cause marked thinning of the bone. The contents of this cyst may be clear and mucinous, or cloudy with degenerated epithelium. A dentigerous cyst is formed as the result of the activity of the paradental cell rests derived from the enamel organ, so that it is

lined by stratified squamous epithelium. The whole of the epithelium must be destroyed or the cyst will recur after removal. The cysts are of course always related to a tooth, usually one of the bicuspids. An unerupted tooth may project into the cyst. This tooth may be supernumerary or one of the permanent set. In the latter ease, which is more common, one of the teeth will be missing.

Adamantinoma.—This is a *rare* tumor of the jaw commencing usually in childhood or early adult life, growing slowly over a course of many years, causing marked enlargement of the bone with rarefaction and thinning of the cortex. Although benign in character it may infiltrate the bone farther than is apparent to the naked eye, so that removal of the tumor may be followed by recurrence. Degeneration with the formation of the pseudocysts is not infrequent. The adamantinoma is an epithelial tumor which arises from the remnants of the enamel organ or from cell rests scattered along the length of the tooth. It might well be called an enamel cell tumor. It is closely related to the dentigerous cyst.

The microscopic appearance varies considerably, but tends to reproduce the structure of the enamel organ. When the reproduction is most accurate it is possible to recognize an outer layer of columnar cells, the enameloblasts, and a central core of "star cells," *i.e.*, cells with large vacuoles in the cytoplasm and connecting cytoplasmic bridges. In other cases the structure is more epidermoid in type, the cells being arranged in sheets, but isolated clumps of columnar enameloblasts will usually indicate the true nature of the lesion. Degeneration of the center of the cellular mass may produce a gland-like formation which must not be mistaken for adenocarcinoma (Fig. 94).

Similar tumors are found in the stalk of the pituitary, where they are known as suprasellar tumors, and, paradoxically enough, in the tibia. Both the pituitary stalk and the enamel organ arise from the oral epithelium. The extremely rare tumors of the tibia are very much of a puzzle, but may possibly be explained on a basis of abnormal embryonic epithelial invaginations.

Odontoma.—This very rare condition is a composite benign tumor made up of enamel, cementum and dentine. It is a true mixed tumor, as *the enamel is derived from ectoderm, and the cementum and dentine* from mesoderm, and it seems to be a product of disordered growth of the whole tooth germ. The tumor, which is usually in the mandible, is circumscribed by a fibrous capsule, and grows from the root of a tooth in a child or young adult. The corresponding tooth is missing. In a typical case the tumor consists of a fused mass of imperfectly formed tooth, but sometimes there is a fibrous mass in which is embedded rudimentary teeth and their corresponding enamel organs. There is no tendency to cyst formation or rarefaction, and the tumor may closely resemble an osteoma of the jaw.

PARASITIC CYSTS

Hydatid Cysts.—The cystic stage of many parasites is passed in the lower animals, but in man the only one of any importance is the hydatid cyst. This is the larval or cystic stage of the Taenia echinococcus, a tapeworm which passes its adult life in the intestine of the dog. It is·

the smallest of all the tapeworms, measuring less than half an inch in length and possessing only three segments. The head is well armed with two rows of hooklets and four suckers.

The cycle of the tapeworm includes the carnivora and the herbivora. Starting in the intestine of the dog, the eggs are discharged in the feces, contaminate drinking water and green vegetables, and are ingested by man and such herbivora as sheep and cattle. In these animals the parasite passes through the cystic stage, but it can only return to the dog through that animal devouring the infected carcass or organs of an infected sheep or cow. The disease is confined to cattle-raising and sheep-raising countries, where the domestic relationship between men and their dogs is unusually close. It is prevalent in Australia and South America in particular and used to be common in Iceland until preventive measures were instituted.

The ripe segments, crowded with ova, are discharged from the bowel of the dog, and ingested by one of the herbivora. The ova are surrounded by a capsule which becomes dissolved by the gastric juice, and the little embryos are set free. They are absorbed into the radicles of the portal vein, and are carried first to the liver. The liver, therefore, is the organ most commonly infected. If they pass the liver they will lodge in the lungs. Finally, if they pass the lungs they are carried into the systemic circulation and may settle in any organ of the body.

The embryo now develops into a cyst and enters upon the larval stage of its career. The cyst wall is formed of two layers, each of which is characteristic. The outer layer or ectocyst is thick and resembles coagulated white of egg; it is made up of a number of parallel layers like the leaves of a book. The inner layer or endocyst is the germinal layer. From it are budded off new heads or scolices of the tenia. Each scolex develops in a little cup-shaped process known as the brood-capsule there being many scolices in each capsule. One germinal layer may give rise to very may scolices. In addition to forming new heads the endocyst may give rise to numerous daughter cysts, which usually develop within the main cyst, but sometimes outside of it. Within some of the daughter cysts new scolices may arise. Others remain sterile. The irritation of the cyst leads to the development of a well marked fibrous capsule from the organ in which it is situated.

The fluid in the cysts is clear and watery, non-albuminous, neutral and of a specific gravity of about 1.005. It often contains hooklets, and a precipitin reaction may be obtained when the fluid is mixed with the serum of a patient suffering from hydatid disease. In such a patient a wheal is raised by the intradermic injection of hydatid fluid (Cesoni's reaction). The laminated membrane is quite as characteristic as the hooklets. The blood displays a slight degree of eosinophilia, which may be of some diagnostic value. It never becomes marked, and is usually around 5 per cent. It is important to remember that if the cyst suppurates the eosinophilia disappears.

When the embryo dies the cyst ceases to enlarge, and secondary changes may occur. It may rupture externally, into a serous cavity, or into a hollow viscus; suppuration may occur with the formation of an abscess; or the cyst contents may become converted into a gelatinous mass and

the wall become calcified. Leakage of the fluid may give rise to a rash resembling urticaria or scarlet fever, due to absorption of toxic products.

The commonest *site* of a hydatid cyst is the liver, then come the lungs, but it may occur in almost any part of the body, and the brain is by no means exempt. In the abdomen it is liable to be mistaken for other causes of enlargement, such as ovarian cyst, and I have known the abdomen to be opened in search of a carcinoma, only to reveal a large hydatid cyst in the ileo-cecal region.

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CHAPTER X

NECK, SALIVARY GLANDS AND ESOPHAGUS

THE NECK

The chief diseases of the neck are inflammation, cysts and tumors.

Inflammation.—Inflammation in the neck deserves special consideration because of its tendency to become diffuse, and its relation to the deep cervical fascia. It spreads throughout the neck as a diffuse cellulitis, comparatively harmless when superficial to the cervical fascia, but fraught with the gravest consequences when deep to that structure.

Pus is formed in large amount, but being unable to escape it surrounds the great vessels and trachea, and may make its way into the mediastinum. It is under great pressure, so that the tissues feel hard and brawny. Respiration is interfered with through pressure on the trachea, and edema of the glottis is a common cause of death. To the severer forms of the condition the term *Ludwig's angina* is applied.

The disease usually occurs as a complication of one of the acute fevers such as scarlet fever or erysipelas, and the common infecting organism is Streptococcus pyogenes.

Localized inflammations due to Staphylococcus aureus are common at the back of the neck in the form of boils and carbuncles, owing to the constant irritation of the collar.

Tumors and Cysts.—Many of the tumors and cysts of the neck are of developmental origin. In the second week of embryonic life five outpouchings occur from the internal lateral walls of the foregut; these are the branchial pouches. At the same time the external ectoderm becomes indented over the pouches to form the branchial grooves. The pouches and grooves approach one another, being finally separated only by a membrane; in fishes this arrangement forms the gill clefts. The mesoderm is pushed aside into six rounded bars, the branchial arches. From the third pouch on either side two tubules descend into the mediastinum to form the thymus; they lie lateral to the thyroid and in front of the carotid sheath. The remnants of this tubule have been demonstrated in the adult (Wenglowski). Bronchial cysts and fistulae are formed from the thymic duct (third pharyngeal pouch). If only portions of the pharyngothymic duct disappear, lateral cysts develop. If an external opening forms on the skin and the entire duct persists, a complete lateral fistula develops. Tumors and cysts may conveniently be considered together, for many of the cysts are cystic tumors. They may be mesial or lateral.

Mesial Cysts.—A cyst or tumor in the middle line of the body, whether in the neck or elsewhere, is almost certain to be developmental in origin. In the neck such cysts may be thyroglossal or dermoid in origin. A *thyroglossal cyst* or tumor arises from the vestigial remains of the thyroglossal tract, which passes from the foramen cecum at the base of the

tongue to the isthmus of the thyroid gland. If the tumor is solid, the structure is that of the thyroid gland, if cystic the cavity is lined by columnar epithelium. These masses are much commoner below than above the hyoid bone, but they may occur at the back of the tongue. They are firmly attached to the hyoid. A *dermoid cyst* is a sequestration dermoid formed by inclusion of epidermal elements during closure of the midline of the neck. The cyst wall is therefore lined by stratified epithelium of epidermoid type, with its associated hair follicles, sweat glands, and sebaceous glands. The cyst contains sebaceous material produced by these glands.

Lateral Cysts.—A lateral cyst or tumor may be a branchial cyst, a cystic lymphangioma or one of the numerous varieties of cervical lymph node enlargement which will be described in a subsequent chapter. Enlargements of the thyroid gland are also not considered in this connection.

A *branchial cyst* is of developmental origin, arising from remnants of the thymic duct (third pharyngeal cleft). Although congenital, the cyst does not usually appear until puberty, because the fluid which it contains accumulates very slowly. It forms a rounded swelling below and behind the angle of the jaw, and when small is often mistaken for a tumor or an enlarged gland, but becomes softer with increase in size. It may attain the size of an orange. The cyst is usually lined by squamous stratified epithelium, but if it arises from the internal branchial furrow, the epithelium may be columnar or ciliated. A striking feature of the wall is the presence of a large amount of lymphoid tissue (Fig. 95). The contents are viscid and mucoid, and may contain cholesterol crystals in large numbers.

Fig. 95.—Branchial cyst; abundant lymphoid tissue. × 75.

A *branchial fistula* may be more properly called a sinus, for it usually has only one opening, situated at some point along the anterior border of the sternomastoid, commonly at the level of the angle of the jaw. It is derived from the second branchial cleft. If there is an internal opening it is usually in the tonsillar pit. In rare cases there is an internal opening, but no external one. The tract is lined by epithelium which is likely to be columnar and ciliated in the inner portion, squamous and stratified in the outer. Here again there is an abundance of lymphoid tissue in the wall.

Cystic Lymphangioma.—This condition, known also as cystic hygroma and lymphatic cyst, has already been described in the chapter on Tumors. It is not uncommon disease in children, but owing to its tendency to spontaneous cure it is seldom met with in the adult. The common position

is the anterior triangle of the neck. It is more thin-walled and translucent than the branchial cyst. It probably arises from sequestrations of lymphatic tissue derived from primitive jugular sacs which failed to join the regular lymphatic system.

Cervical Gland Enlargement.—A great variety of conditions may give rise to lymph node enlargement in the neck and these will be discussed in connection with diseases of the lymphatic system. They may be divided into four main groups: (1) acute or chronic inflammation (from tonsil, tooth, jaw), (2) infective granuloma (tuberculosis, secondary syphilis, rarely primary syphilis), (3) lymphoblastoma (Hodgkin's disease, lymphosarcoma, leukemia), and (4) secondary carcinoma (from lip, tongue, mouth, larynx, nasopharynx, esophagus). Special mention may be made of the transitional-cell carcinoma, because the primary lesion is small and tucked away in the nasopharynx or pyriform sinus, whilst the infected lymph nodes in the neck attain a great size and are apt to be regarded as the primary seat of disease.

Cervical Rib.—This condition is not uncommon (1 to 2 per cent). The accessory rib arises in relation to the transverse process of the seventh cervical vertebra, and may be represented by a mere knob of bone, or by a fully-formed rib which articulates with the vertebra, and may be attached by its anterior end to the first rib or even the sternum. The importance of the condition lies in the fact that it may cause a pressure neuritis of the brachial plexus. The symptoms seldom develop before the age of twenty, almost never before fourteen. It is commoner in women. The development of symptoms depends on the length and direction of the rib. If it is small and projects to the side it is not likely to cause pressure, but if it is long and curves forward, the lower trunk of the plexus will cross the rib and is liable to be pressed upon. There must also be accessory factors, for even a well-developed supernumerary rib may produce no symptoms, and development of symptoms may be delayed till middle life or later. The elongation of the neck during adolescence probably leads to stretching of the plexus, and loss of muscle tone which follows an acute illness by allowing sagging of the arm probably produces a similar result.

The pressure effects are sensory, motor and sympathetic. The *sensory* symptoms are pain along the ulnar (occasionally the radial) side of the forearm, paresthesia, and even anesthesia. The *motor* symptoms are weakness of the small muscles of the hand. *Sympathetic* symptoms due to pressure on the sympathetic fibers of the first thoracic nerve take the form of pallor and flushing of the fingers; gangrene has even been reported.

Tumor of the Carotid Body.—Arising in the bifurcation of the common carotid artery about the time of puberty there occasionally occurs a firm, rounded, slowly growing tumor which is liable to be mistaken for many conditions. This is a carotid body tumor. The growth may be regarded as benign, growing slowly for many years, but lymph node involvement has been recorded. There is an intimate relation between the tumor and the carotid vessels; sometimes the latter may pass through the middle of the tumor. This relationship is of great surgical importance, for if the internal carotid artery has to be divided the mortality is high owing to cerebral edema and necrosis of brain tissue. The average mortality is given as 30 per cent. For this reason it seems better not to remove this benign

tumor if it necessitates division of the internal carotid artery, and to treat the lesion by radiation.

Microscopically the picture is a varied one. In the only example which I have studied the cells were large, pale, polyhedral, and arranged, in sheets and groups (Fig. 96). The structure is usually described as that of an alveolar perithelioma. The condition should be regarded as a tumor of the chromaffin system to which the carotid gland belongs, a chromaffinoma. In some of the reorded cases, however, there has been marked overgrowth of the vascular endothelium.

Rare Conditions.—Blood cysts, beginning as a diverticulum of a large vein and later becoming isolated, may occur.

Cysts may arise in connection with the suprahyoid and thyrohyoid bursae.

Tumors, either innocent such as lipoma (circumscribed or diffuse), fibroma, or osteoma, or malignant such as sarcoma or carcinoma, may occur primarily in the neck. A carcinoma may arise in the remnants of one of the branchial clefts.

Fig. 96.—Carotid body tumor. × 500.

THE SALIVARY GLANDS

The most important pathological conditions affecting the salivary gland are acute inflammation and tumors. The parotid is the common site of these disturbances, but the submaxillary and sublingual may on occasion be involved also.

Acute Inflammation.—Inflammation of the parotid may be nonsuppurative or suppurative.

The *non-suppurative* form is known as mumps. The gland, usually in children, becomes acutely inflamed, hot, swollen, and tender, but seeing that the condition is not due to pyogenic organisms, it ends by resolution, not by suppuration. An associated acute inflammation in the testicle is a fairly common complication, and in some cases this may be followed by atrophy of the testicle.

In the *suppurative* form the infection may come from the blood stream, as in acute fevers or in pyemia, or from the surrounding structures. Infection from the mouth by way of Stensen's duct is the most obvious and important method. The most frequent invaders are Staphylococcus aureus and the pneumococcus.

Suppuration usually occurs about the third or fourth day. Owing to the dense fascia which lies superficial to the gland the pus may extend upwards, downwards, or inwards (one variety of retropharyngeal abscess), but not to the surface.

Mixed Tumors.—These tumors occur in the salivary glands, mucous membrane of the mouth, and soft palate. By far the commonest site is the parotid gland, so that the condition is often called a "parotid tumor." It is a benign lesion, but it may recur after incomplete excision, and may then become locally invasive, producing erosion of the bone. Spontaneous malignant change is very rare. It usually occurs between the ages of 20 and 40, but one of our cases was a child of four. Growth is slow, and may extend over a period of many years, but may cease at any time. The lymph nodes are seldom involved unless the tumor is interfered with, but unsuccessful removal may be followed by invasion of the cervical glands.

Structure.—The tumor may grow from the substance or the surface of the parotid, and is very firm in consistence. When growing from the

Fig. 97.—Mixed tumor of parotid, with glandular tissue, mucoid tissue and cartilage. × 200.

palate it forms a hard tumor which may obstruct the pharyngeal opening. The microscopic structure is varied and mixed, the chief constituents being: (1) strands of epithelial cells which may show a glandular arrangement, (2) mucoid connective tissue, (3) cartilage, and (4) lymphoid tissue. The highly mucoid tissue is particularly characteristic (Fig. 97). It is not possible to determine from microscopic examination whether the lesion should be regarded as benign or as taking on malignant characteristics.

There are two principal views which seek to explain the great diversity of histological structure, a diversity which it is impossible to represent in a single illustration. The first of these is that the mixed tumors are embryonic tumors of local origin. Li and Yang, whose excellent illustrations should be consulted, give the arguments in favor of this view. The embryonic rests from which these tumors are supposed to be derived are

formed, along with the salivary and oral glands, from invagination of the oral ectoderm.

The second view is that the tumors are adenomas of the salivary glands rather than mixed tumors. It is suggested that the cartilage is not true cartilage but pseudocartilage. The tumor epithelial cells produce mucin, and this forms the ground substance of the mucinous "connective tissue." This myxomatous material, which stains well with mucicarmine, is homogenous like cartilage, and the cells which it contains may lie free in small spaces around which there may be a fibrillar condensation, so that a pseudocapsular appearance closely resembling cartilage is produced. It is possible, however, that true cartilage may be formed from epithelium, as has been shown to occur in malignant mixed tumors of the mammary gland, where the mucoid matrix derived from the epithelium may develop into cartilage (Allen). Mucin and cartilage are very similar chemically. In spite of the law of the specificity of the germ layers it would appear that if a cell is sufficiently immature it possesses a plasticity which enables it to be molded by its environment. The attributes of a cell depend on the dictates of its environment. Simard reports a mixed tumor of the palm of the hand in which the cartilage appeared to develop as a stromal reaction to epithelial degeneration.

Hellwig points out the resemblance of mixed tumors to the developing notochord, and suggests that these tumors are derived from misplaced elements of that structure. The notochord is in contact with the buccopharyngeal membrane, and on the rupture of that membrane the cells of the two structures may be intermingled. It

Fig. 97.—Adenolymphoma of parotid × 110.

may be noted that the notochord comes into intimate relation with the developing parotid gland, the submaxillary gland, and the palate, the three common sites of mixed tumors.

Some of the tumors may arise from embryonic rests, but it is probable that the great majority are of the nature of benign epithelial growths.

Carcinoma.—This usually occurs in the parotid gland. It may be adenocarcinomatous, medullary or anaplastic. It differs from the mixed tumor in that it grows rapidly from the beginning, soon involves the regional lymph nodes, and sets up distant metastases.

Adenolymphoma.—This is a rare tumor of the salivary glands, usually the parotid. It is a benign tumor of males over middle age, seldom in females. It consists of a mixture of glandular and lymphoid tissue, the latter presenting active germ centers (Fig. 98). There may be cystic spaces with papillary projections.

Uveo-parotid Tuberculosis.—A particularly fibrosing and noncaseating type of tuberculosis may effect both parotid glands and the uveal tract of the eye (iridocyclitis). The submaxillary and lacrimal glands may also be enlarged, so that the lesions may be mistaken for Mikulicz's disease. A slight degree of pyrexia is common, and the clinical condition is known as uveo-parotid fever. The disease is seldom fatal. Many, perhaps the majority, of these cases are now regarded as being examples of sarcoidosis (see page 586).

Mikulicz's Disease.—This is a very rare condition in which there is enlargement of the three salivary glands and the lachrymal gland. The glands are replaced by small round cells, and the condition may be regarded as a localized form of lymphoblastoma.

THE ESOPHAGUS

A patient who comes to a surgeon complaining of esophageal symptoms such as difficulty in swallowing and regurgitation of food may have a perfectly healthy esophagus pressed upon from without by a tumor or an aneurism. It is always wise to consider the possibility of aortic aneurism before passing a bougie down the esophagus.

If these outside conditions can be excluded the patient is suffering, in order of frequency, from (1) carcinoma, (2) stricture either cicatricial or spasmodic, or (3) an esophageal diverticulum.

Carcinoma.—Cancer of the esophagus, one of the most hopeless conditions with which the surgeon has to deal, resembles cancer of the tongue in that it occurs in about 80 per cent of cases in men over 40 years of age. In many cases raised white areas may be seen on the wall of the esophagus at some distance from the tumor, recalling the condition of leukoplakia.

The tumor does not begin at any random point of the tube, but at one of three definite sites: the upper end, the level of the bifurcation of the trachea, and the lower end. The second is the most common site (Fig. 99), the first is the most rare. As in the case of malignant disease in the stomach, the intestine, the gall bladder, and other situations, cancer of the esophagus may appear in one of three forms: (1) a flat infiltrating ulcer, (2) a more bulky polypoid mass, or (3) a diffuse infiltration. It commences in the mucous membrane as a squamous epithelioma, although in rare cases a columnar-celled carcinoma may arise from the mucous glands. Cornification is little if at all marked, and epithelial pearls are usually absent.

The disease slowly encircles the esophagus (Fig. 100). As Chevalier Jackson points out, it is a mild, slow, and for a long time a purely local process. Metastases occur mainly in the regional lymph nodes, but occasionally in distant organs. The position in which the cancer occurs bears some relation to the direction of the metastases. If at the upper end of the esophagus, the lower and deep cervical nodes will be involved, together with those in the superior mediastinum. When it occurs in the middle third, the nodes involved are those around the bifurcation of the trachea. When the tumor is in the lower third the metastases commonly occur below the diaphragm through the celiac chain of nodes. In Clayton's series of 41 cases metastases occurred below the diaphragm in 22. In 11 of these cases the liver was involved.

Spread of the disease involves the surrounding structures. The trachea or a large bronchus may be penetrated, causing aspiration pneumonia. If the lung is involved, an abscess or gangrene may develop. Perforation of the aorta leads to fatal hemorrhage. There may be perforation into the mediastinum with resulting subcutaneous emphysema or abscess formation. The left recurrent laryngeal nerve may be involved as it passes round the arch of the aorta. A tumor at the upper end of the esophagus may spread into the pharynx, one at the lower end may spread into the stomach.

Symptoms occur very late in the disease. The most common symptom is difficulty in swallowing. As the diagnosis is made so late, the average duration of life after the appearance of the first symptoms is only about 7 months. Chevalier Jackson claims that by means of the esophagoscope

Fig. 99.—Roentgenogram of carcinoma of esophagus in middle third.

Fig. 100.—Carcinoma of esophagus with extreme stenosis.

a carcinoma can be diagnosed when it is no larger than an orange seed. As this is the only method of making a really early diagnosis, it should be employed at once in every case of suspected carcinoma of the esophagus.

In an analysis of 108 autopsy cases Mathews and Schnabel found that 20 per cent were of a non-stenosing type. Dysphagia was rare, the principal symptoms being loss of weight, pain in the chest, vomiting, cough, and hoarseness. The fatal course was shorter than in the stenosing variety.

Cicatricial Stricture.—The formation of scar tissue giving rise to stenosis is due generally to the swallowing of corrosive fluids, often taken for suicidal purposes, and occasionally to the laceration produced by impacted

foreign bodies, such as tooth-plate. Peptic ulcer may occur at the lower end of the esophagus owing to the presence of heterotopic gastric mucosa. Healing of such an ulcer with fibrosis may cause an extreme degree of stricture (Fig. 101).

The destruction of the mucosa is naturally most marked at the narrowest points of the esophagus, so that the stricture generally occurs at the upper or lower ends. Dense scar tissue is formed which encircles the esophagus, but may extend for some distance up and down the tube and by its contraction produces an extreme degree of stenosis.

In most of the hollow muscular tubes of the body partial (not complete) obstruction is followed by dilatation and hypertrophy of the part above, and collapse and atrophy of the part below. This is rarely seen in the esophagus. The probable reason is that the food collecting above the stricture is so easily ejected that dilatation of the tube has no time to occur.

Fig. 101.—Stricture of esophagus due to peptic ulcer.

Cardiospasm; Achalasia.—This is a functional form of stricture at the lower end of the esophagus, in which no organic lesion can be found in the esophageal wall, and yet swallowing becomes more and more difficult. It usually occurs in women. The onset is insidious, and symptoms manifest themselves in early adult and middle life, but they may appear for the first time in old persons. In distinction to what is found in organic stricture, there is a remarkable dilatation of the esophagus above the site of the obstruction (esophagectasia) with hypertrophy of the circular coat of muscle (Fig. 102). The esophagus may be lengthened as well as greatly dilated. The stretched mucous membrane may show secondary inflammatory changes. In the X-ray picture the lower end of the esophagus (filled with barium) has a characteristic conical or pointed appearance, quite different from what is seen in organic stricture.

The exact *nature of the condition* is still a matter of uncertainty. During life there appears to be distinct narrowing of the esophagus at the point where it passes through the diaphragm, but there is no thickening of the wall nor dilatation of the lumen at this point. The modern view is that the condition is due to some disturbance of the neuromuscular mechanism of deglutition, an imbalance between the vagus (motor) and sympathetic (inhibitory) nerves. The name cardiospasm suggests that spasm due to overaction of the vagus is the essential factor, but it appears more probable the condition is an achalasia, an inability of the circular muscle to relax, due to preponderance of sympathetic control. Degenerative lesions in Auerbach's nerve plexus in the wall of the esophagus have been described.

Other possible examples of achalasia are Hirschsprung's disease (inability of the rectal sphincter to relax), esophageal (pharyngeal) diverticulum, and the so-called Plummer-Vinson syndrome. In the latter condition there is *dysphagia with anemia* usually occurring in middle-aged women but sometimes in men. In this case there is failure of the cricopharyngeous sphincter between the pharynx and esophagus to relax during deglutition. The mucosa of the pharynx and tongue becomes very dry. The anemia may be due to the long-continued condition of semi-starvation. The great practical importance of the achalasias at either end of the esophagus is that they may be mistaken for malignant stricture.

Diverticula.—Diverticula of the esophagus may be divided into posterior and anterior varieties.

The *posterior* variety is the more common and important. It occurs at the junction of the esophagus and pharynx; indeed it is a pharyngeal rather than an esophageal diverticulum. It occurs most frequently in men past middle life. As with other diverticula, hernias, and aneurisms, two etiological factors suggest themselves—weakness of the wall and increased pressure within. It has been the custom to suppose a congenital weakness of the pharyngeal wall, but for this there is no real foundation. The important factor is therefore probably prolonged abnormal intrapharyngeal tension. In some cases this may be due to organic stricture, but far more frequently it appears to arise from incoördinate action between the propulsive and sphincteric elements of the pharyngeal muscle. Here again there is imbalance of the neuromuscular mechanism, in other words an achalasia. Chevalier Jackson speaks of the "cricopharyngeal pinchcock."

Fig. 102.—Dilatation of esophagus due to cardiospasm.

In performing esophagoscopy without general anesthesia, the cricopharyngeus muscle is at first tightly contracted. Jackson regards the barrier presented to the advance of the bolus by the unrelaxed cricopharyngeus as the functional factor that herniates the pharyngeal wall.

7

Gradually a protrusion of the mucous membrane of the lower part of the posterior wall of the pharynx occurs between the oblique and transverse fibers of the cricopharyngeus muscle. The forward displacement of the upper end of the esophagus still further directs the food back with ever increasing enlargement of the diverticulum. It projects downward behind the esophagus as a sac into which passes much of the food, and which by its pressure on the esophagus may give rise to great difficulty in swallowing. The X-ray picture is highly characteristic.

The *anterior* variety occurs at the level of the bifurcation of the trachea. It is produced by the traction of fibrosing tuberculous nodes which have become adherent to the esophagus, and is of little importance. The posterior form is a pulsion diverticulum, the anterior form a traction diverticulum.

Rare Conditions.—Syphilis, tuberculosis, or even typhoid fever may in rare cases produce ulceration of the mucous membrane of the esophagus, with the subsequent development of a stricture.

A peptic ulcer may occur at the lower end of the esophagus. This is probably due to the occasional presence of heterotopic islands of gastric mucosa, and is therefore comparable with the peptic ulcer which sometimes occurs in Meckel's diverticulum. Healing of such an ulcer may cause stricture of the esophagus.

Various innocent tumors may occur, such as fibroma, myoma, lipoma, and warts. The fibroma is often pedunculated, and such polypi are found chiefly in the upper part of the esophagus.

Sarcoma is very rare. It may be round-celled or spindle-celled.

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THE THYROID GLAND

The thyroid is developed as a downgrowth from the ventral wall of the pharynx between the first and second pharyngeal pouches. The stalk connecting the embryonic thyroid with the pharynx becomes constricted to form the thyroglossal duct, which at birth is represented only by the foramen cecum, a dimple at the posterior part of the tongue which marks the site of the former opening of the duct.

Portions of the gland may become displaced during the course of development. A nodule occurring at the base of the tongue is called a *lingual thyroid.* Portions detached during the process of descent may form *accessory thyroids* in the neck. Finally, segments of the thyroglossal duct may fail to be obliterated, and may at any subsequent period give rise to *thvroglossal cysts* owing to the secreting power of the vestigial mucosa.

The thyroid increases in weight with the years, reaching its maximum in early adult life, then gradually decreasing till the end of life. The acini increase or decrease in size with the weight of the gland. In infancy the acini are small and contain little or no colloid. They increase in size with the years till early adult life. The senile gland may resemble that of the infant. The series of pictures in Rice's paper show very well the structure at the different age periods. Nodules may be present in an otherwise normal gland. They probably represent a physiological response to stimuli. They arise at puberty or later, the incidence increasing rapidly with age. About 30 per cent of glands contain nodules at the age of thirty (Rice). Thus 30 per cent of patients with Graves' disease at this age will present a nodular thyroid. If nodules are present in a toxic goitre, they are not necessarily the cause of the toxic symptoms.

GOITRE

The word goitre at the present time is used very loosely. We discuss goitre as if it were a disease, whereas it is merely an enlargement of the thyroid gland. On the other hand we divide goitre into such classes as colloid goitre, adenomatous goitre, and exophthalmic goitre, regarding them as separate diseases.

The key to the goitre problem, or at least a possible key, is to be found in the processes of hyperplasia and involution. Both of these processes have been carefully studied in the animal experimentally, by Marine in particular. When three-quarters of the thyroid of a dog are removed the remainder soon begins to show changes which may be classed as hypertrophy and hyperplasia. The remnant becomes larger until the original size of the gland may be restored. At the same time there is proliferation of the epithelial cells, a true hyperplasia. The histological changes are briefly as follows. The vascularity of the gland is markedly increased. The

epithelium lining the acini becomes tall and columnar, the nucleus occupies only the center of the cell, and numerous mitotic figures testify to the activity of cell division. The cytoplasm stains feebly, and contains many prosecretion products in the form of granules and globules which cause the sides and the apex of the cell to bulge. Suitably stained sections show a great increase of mitochondria in the cells. In order that the acinus may accommodate the increased number of cells the acinar space becomes enlarged, and soon the proliferating epithelium is seen to project into this space in the form of processes, till the acinus comes to assume an almost solid appearance. At the same time the colloid changes in character. It no longer appears dense and stains intensely with eosin, but becomes vacuolated, thinned, and finally disappears. The store of iodine varies inversely with the hyperplasia, and becomes more and more depleted as

Fig. 103.—Involuting thyroid, showing the enormous size of some of the acini. × 30.

the hyperplasia increases. There is an increase in the lymphocytes of the stroma.

The process is evidently one of compensation. The remaining portion of the thyroid has to perform more work, to supply more iodine to the body in the form of thyroxin, and therefore draws upon the accumulated store in the colloid of the acini. The acinar cells undergo what may be termed a work hyperplasia. This is the process which is seen in the early stage of a simple goitre, a process which is to be interpreted once more as a compensatory effort in response to a physiological stimulus. The same process of hyperplasia is seen in the various forms of toxic goitre, but whether it is to be regarded here also as of essentially the same nature we are really not in a position to say. The thyroids of animals living under domesticated conditions often show a marked degree of hyperplasia.

Involution is the natural complement of hyperplasia. In the experi-

mental animal it may be observed to occur as a result of exhaustion of
the hyperplastic process. At any time it may readily be induced by the
administration of iodine to the animal. When the iodine is stopped the
hyperplastic at once reappears. It seems that as long as there is an abun-
dant supply of the raw material the gland can work at a normal rate, but
when the supply falls below a certain level, only a feverish activity on the
part of the gland will suffice for the normal metabolic processes.

The histological picture of the involution process is quite as charac-
teristic as that of hyperplasia. The acini are no longer filled by the pro-
liferated buds of epithelium, but some of these still project as attenuated
sprigs. Many of the acini remain markedly distended, and are lined by
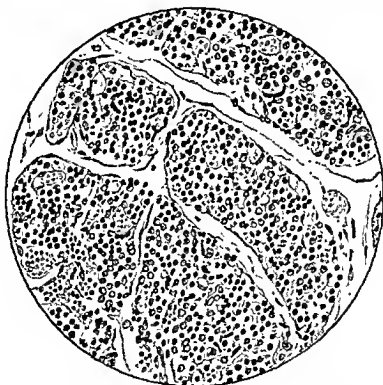
Fig. 104.—Fetal thyroid. The normal tendency to lobulation is well seen at this stage of
development.

a low cubical or flattened epithelium (Fig. 103). The colloid reaccumulates
in the acini, and the vascularity decreases. The stroma is now seen to be
increased and fibrous, and large bands may run through the section.

During life the thyroid is continually being acted on by stimuli of
various kinds, chemical, bacterial, and psychic, which tend to induce
hyperplasia. When the action of these ceases, involution sets in. The
involuted gland may again become the seat of hyperplasia, only to be
followed again by involution. It is evident, therefore, that many of the
glands examined will bear the marks of this cyclical process.

Rienhoff has shown that the alternating phases of hyperplasia and
involution serve to explain the development in man of the nodules in the
thyroid which are commonly called adenomas. When a patient with the

diffuse hyperplastic goitre of Graves' disease is given Lugol's solution, marked involution rapidly occurs. But the process is not uniform. Some lobules resist the involution process, whilst others show a condition of hyperinvolution with dilated acini overdistended with dense colloid. The fibrous septa which normally separate the lobules become thickened, and large colloid areas are formed surrounded by a wide zone of fibrous tissue with compression and even obliteration of the surrounding acini. This is merely an intensification of the normal tendency to lobulation, which is particularly well seen in the fetal thyroid (Fig. 104). Such an area becomes demarcated from the rest of the gland and forms what has hitherto been known as a colloid adenoma (Fig. 105). This view brings the adenomata, or at least many of them, into line with the general pathology of goitre. They are seen not to be true tumors at all, but merely the result of the

Fig. 105.—Colloid nodule developing in a diffuse colloid goitre. × 30.

hyperplasia-involution cycle. With each exacerbation the involuted tissue goes through the same cycle once more, and with each successive involution the nodule becomes larger. In a small number of cases (under 10 per cent) the nodules appear to be true neoplasms. They show no evidence of hyperplasia or involution, being composed of epithelial cells arranged in narrow anastomosing strands.

The Pathogenesis of Goitre.—Goitre is an enlargement of the thyroid gland occasioned in the first place by hyperplasia which may be followed later by involution. If the hyperplasia has not gone too far, the gland may be restored to an approximately normal size as the result of involution. On the other hand it may remain permanently enlarged even though it is in a resting or colloid condition. Both of these states come under the heading of goitre, but it is evident that in discussing the problem of pathogenesis we are only concerned with the production of the hyper-

plasia. In the earlier part of this chapter we have also pointed out that the ordinary adenomata of the thyroid are probably merely local manifestations of the biphasic hyperplasia-involution cycle, although true innocent tumors do also occur.

It is evident therefore that in searching for the cause of goitre we are searching for the cause of thyroid hyperplasia. But there is no reason why there should only be one cause. As there are many causes of necrosis and many causes of inflammation, so there may be many causes of thyroid hyperplasia.

There is one form we can be certain of, namely compensatory hyperplasia. When a large part of the thyroid in an animal is removed, the remainder shows a marked hyperplasia, a picture indistinguishable from that of exophthalmic goitre in man. This, of course, is purely compensatory; the work of the remaining portion of the gland is speeded up to meet the requirements of the body.

If iodine is completely withheld from the food of an animal the same hyperplasia may be observed. Although the mechanism here is not quite so apparent, it appears to be safe to regard this hyperplasia also as compensatory in character. Hyperplasia may also be induced in fish by contaminating the water in which they are kept, as in Gaylord's experiment in which trout were kept in a series of tanks each of which drained into the tank below, and the proportion of goitre increased in each successive tank. In the water above the tanks the fish showed no goitre, but those in the first tank showed 3 per cent, in the second tank 8 per cent, in the third tank 45 per cent, and in the fourth tank 84 per cent. Here the etiological factor is still more doubtful; it may be a matter of bacterial infection in the intestinal tract with the production of toxins which stimulate the thyroid to hyperplasia, or the bacteria may deplete the iodine of the water, so that the hyperplasia may be due to iodine insufficiency. McCarrison's well known observations on the incidence of goitre in villages along the streams in the mountains of Gilgit confirm in man what Gaylord observed in the fish.

McCarrison has shown that thyroid hyperplasia may be produced in other ways than by withholding iodine from the food. A diet containing an excess of fat will produce hyperplasia even though an animal be supplied with an abundance of iodine. A similar condition is produced in young rats fed on a diet containing 60 per cent of white flour or vitamin-poor carbohydrate with 20 per cent or less of protein—fats, salts, iodine being present in adequate amount. McCarrison is of the opinion that this type of goitre will be found sporadically among white flour-eating peoples, who will be prone to develop Graves' disease provided they are exposed to such additional factors as pregnancy, lactation, fright, or acute infectious disease. This introduces the idea of a multiplicity of factors being responsible for the development of goitre in a given case.

Webster and Chesney have shown that when young rabbits are fed on a diet rich in cabbage they develop a marked degree of goitre, and the thyroid may show a considerable degree of hyperplasia, which is probably compensatory in character. According to Marine the active principle in the cabbage is a cyanide. Thyroid hyperplasia and even exophthalmos

may be produced in young rabbits by the injection of cyanides, which greatly lower the oxidation in the tissues.

Remarkable changes in the structure of the thyroid can be produced experimentally in a short time as the result of infections and toxemias, as Womack and Cole have pointed out. If the stimulus is very marked there may be intense desquamation of epithelium and loss of colloid in the course of 18 hours. These intense changes which occur as the result of infection may be almost entirely prevented by giving large doses of iodine. The desquamative changes are followed by marked evidence of repair.

The goitre of adolescence, a form of endemic goitre, appears to be a response to iodine deficiency. Certain it is that the administration of minute doses of iodine effectively prevents its occurrence. Apparently the lack of iodine may be absolute or relative. In the first case there is a deficiency of iodine in the food or water. In the second the supply may be adequate for ordinary purposes, but not for the increased demand of adolescence and puberty. We suppose that there is such an increased demand, although we are ignorant of the exact rôle at this particular period of the iodine or the thyroxin into which it is converted.

The thyroid may become enlarged at other periods of special stress, notably during pregnancy and lactation. With each successive pregnancy the thyroid may become enlarged, only to regress in the intervening periods.

All such hyperplasias may be regarded as compensatory and therefore in a sense physiological. They are seen through all the vertebrates, being particularly marked in fishes. It may be said that whenever the iodine content of the thyroid falls below 0.1 per cent the gland undergoes hyperplasia. Such hyperplasia is not necessarily nor even commonly associated with symptoms of hyperthyroidism. In myxedema and cretinism there may be quite a marked compensatory hyperplasia, whilst the patient shows evidence of thyroid insufficiency.

From what has been said it is evident that the factors responsible for both the hyperplastic and the colloid forms of goitre must be very similar. A colloid goitre is merely an end result of a hyperplastic goitre in which the hyperplasia is usually of a mild form. The majority of adenomatous goitres are of a similar origin, being merely a local expression of the hyperplasia-involution cycle. In a small number of cases, less than 10 per cent of all adenomatous goitres, the adenoma appears to be a true neoplasm and therefore of entirely different origin.

What may be called the *geographic pathology* of goitre must be taken into consideration when reading accounts of goitre from different parts of the world. North American goitre is very different from the goitre of the mountain endemic regions such as the Alps and the Himalayas, and in different parts of Europe the type of goitre varies widely. Swiss goitre is characterized by large nodules with much degeneration and compression of the surrounding thyroid, causing more or less severe hypothyroidism or even cretinism. In de Quervain's clinic in the centre of the Swiss goitre belt 93 per cent of the goitres are nodular and only 7 per cent diffuse. On the German coast, on the other hand, 68 per cent are diffuse and only 32 per cent nodular. In the mountain regions the goitres are

mostly of the microfollicular or so-called "parenchymatous type," whereas on the plains they are of the macrofollicular or colloid type. North American goitres differ from the goitres of the mountain endemic regions in the relative frequency of diffuse enlargement and of Graves' disease and nodular toxic goitre. The type throughout North America is fairly uniform. Hellwig's excellent paper may be consulted for further details.

The Classification of Goitre.—From the pathological point of view the present method of classifying goitre is far from satisfactory. Goitres are usually divided into three main groups, which are regarded as being entirely distinct entities. The first is known as simple or endemic (colloid) goitre, the second as adenomatous goitre, the third as exophthalmic goitre. With the exception of the second, these names are purely clinical and have no pathological connotation. The second is certainly pathological, but it is unjustified, for the nodules are not adenomata in the pathological sense.

A pathological classification should attempt to give some idea of the actual condition of the thyroid. The more one sees of goitre, the less is one inclined to subdivide the lesions too minutely. If the reader will take a series of cases and study a number of blocks from each thyroid, he will be surprised to find how varied are the lesions in any one gland. A simple or colloid goitre is supposed to be one in which the gland is in a completely resting condition, and yet evidence of hyperplasia can nearly always be found if it is looked for. Exophthalmic goitre is characterized by a general hyperplasia, but colloid areas indicating involution are found in all but the most fulminating cases. Finally, adenomata when well developed form a striking gross feature, but more or less complete localization and encapsulation of areas can be found in glands in which the enlargement to the naked eye appears to be quite diffuse. It is not too much to say that quite often in a single section one can see areas characteristic of exophthalmic goitre, of colloid goitre, and of adenomatous goitre. The differences are quantitative rather than qualitative. The morbid anatomical picture depends upon the balance between the processes of hyperplasia and involution, upon the extent to which the hyperplasia has gone before involution has set in, and upon the degree of localization of the hyperplastic and the involutionary processes.

As a matter of fact the difficulty is even more fundamental than has been suggested, for the structure of the normal thyroid gland is itself very variable. Thyroids removed at routine autopsies seldom show the "normal" picture of the text-book of histology. It may be urged that most of these patients have suffered from some infection or toxemia, terminal or otherwise, which may have left its mark on the sensitive gland. But if the thyroids from a series of cases of sudden death be examined, the same diversity of structure will be found, and these cases may present characteristic examples of colloid, nodular and hyperplastic goitre.

For purposes of description and recording it is convenient to divide the cases up into certain groups. As this book is written from the standpoint of pathology the groups will be named as follows: (1) diffuse goitre with involution; (2) nodular goitre, in which either hyperplasia or involution may be predominant; (3) diffuse goitre with hyperplasia. It will be

understood that in the first and third forms both hyperplasia and involution will often be combined. In the second form the development of the nodules is an incident, though from the point of view of pressure symptoms it may be an all-important incident, in the general process.

DIFFUSE GOITRE WITH INVOLUTION

Under this heading is included the well defined endemic or simple goitre, the goitre of adolescence, as well as that more vague term, colloid goitre. Like all other forms of goitre it is more common in women than in men, usually appearing about the time of puberty or shortly before that period. As a rule it tends to clear up after a few years, so that its age period may be said to extend from 15 to 25. In regions where endemic goitre is prevalent it tends to appear earlier and to last later in life. It
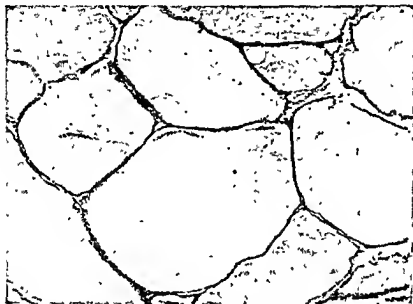
Fig. 106.—Diffuse colloid goitre. The colloid is dense and abundant, and the lining epithelium much flattened. There is no interacinar tissue. × 75.

responds in a remarkable manner to the administration of iodine. According to Plummer, if 10 mg. of thyroxin are given intravenously or a corresponding dose of thyroid extract by mouth, the thrill of a simple goitre in the active stage disappears in from 3 to 6 hours, and the thyroid shrinks rapidly in the course of 24 hours. A goitre of moderate size may disappear completely in a couple of weeks under thyroxin treatment, but when the thyroxin is discontinued the vascular phenomena will return in the course of two or three weeks.

If this form of goitre be examined early in the disease it will be found to show well marked hyperplasia, a hyperplasia which must be regarded as compensatory in character. At the age period at which the goitre of adolescence appears there seems to be a greater demand for thyroid secretion, as a result of which, especially if the supply of iodine is insufficient, there is a hyperplasia of the gland. Young girls with a developing

goitre not infrequently show evidence of thyrotoxicosis which in some cases may suggest a developing Graves' disease. As the demand upon the thyroid lessens the hyperplasia decreases, is replaced by an involutionary process, and the clinical picture may become one of mild hypothroidism.

A colloid condition of the thyroid with enlargement, that is to say a colloid goitre, may develop at any time of life as the result of involution following hyperplasia. The thyroid of exophthalmic goitre during a remission may present the picture of colloid goitre. The same change can be produced, for a time at least, in any hyperplastic goitre by the administration of iodine.

Morbid Anatomy.—The gland is uniformly and diffusely enlarged. It is soft in consistence. The cut surface is uniform in character, amber in color, and presents a finely honey-combed appearance. An excellent idea of the
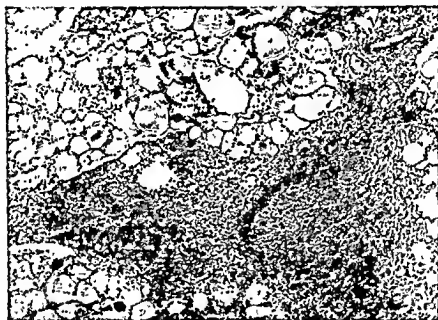
Fig. 107.—Lymphoid hyperplasia in colloid goitre. × 75.

condition of the thyroid can be obtained by viewing the cut surface with a binocular dissecting microscope. When a powerful illuminant such as an arc lamp is used one can see into the depths of the tissue, which is seen to be composed entirely of large spaces filled with clear colloid. Any areas of hyperplasia appear as solid islands surrounded by colloid. This means of examination also shows up the fibrous tissue of the gland, and this tissue may be increased to a degree seldom realized from a study of microscopic sections. Indeed in some cases the groups of acini seem to be embedded in a fleecy mass of cotton wool.

The microscopic appearance at first sight suggests normal thyroid tissue, but more careful examination will readily show evidence of involution and former hyperplasia. Many of the acini are greatly dilated, so that the lining epithelium is correspondingly flattened; they are filled with densely stained colloid (Fig. 106). Other acini are much smaller

than normal. The traces of former hyperplasia can be seen in the form of spurs of epithelium which project into the lumen of the acini like withered branches of a burnt-out tree, mute evidence of a former conflagration. Islands of still active hyperplasia may be found if the search be sufficiently careful. There is no evidence of vascularity, and any vessels that may be seen are compressed by the greatly distended acini.

Such is the classical picture of the resting or involuting thyroid. But great variations will be often be found in different sections and in different parts of the same section, for uniformity is no part of the behavior of the thyroid in disease. The hyperplasia of some areas may be so great that if they alone were examined the case would be taken as one of exophthalmic goitre. Collections of lymphocytes, so characteristic of that condition, may occasionally be seen in a colloid thyroid (Fig. 107). The behavior of the stroma is of particular interest. Under a hand lens or a dissecting microscope commencing lobulation can be made out in many places, and around these lobules the fibrous tissue is becoming thickened. Were the process a little more advanced, definite nodules or "adenomata" would be formed.

Occasionally the rarefied areas, presently to be described in connection with adenomatous nodules, and characterized by wide separation of the acini, dilatation of vessels, hemorrhage, and acinar budding, may be observed in the diffuse colloid thyroid. In one gland, therefore, and even in one section of that gland, one may see areas typical of colloid goitre, of adenomatous goitre, and of exophthalmic goitre. Such evidence should make one very reluctant to consider these three conditions as three separate diseases.

NODULAR GOITRE

The presence of nodular masses in the enlarged thyroid is of very common occurrence. These masses are usually known as adenomata, under the belief that they are true neoplasms. This question has already been discussed in the earlier part of this chapter, where the conclusion was reached that most of these nodules were not adenomata at all, but localized enlargements resulting from hyperinvolution confined to one lobule or a group of lobules.

These so-called adenomata usually make their appearance at the most active period of the life of the gland, that is to say between the ages of 15 and 20. It is not, however, in a normal gland that they appear, but in one which is already the seat of a goitre. The diffuse enlargement may entirely obscure the presence of the adenoma, but the regression of the goitre which follows the use of iodine may allow the nodule to become prominent.

This is the form of goitre which is most likely to be attended by pressure symptoms on the trachea and other neighboring structures. In addition to these local symptoms there may or may not be symptoms of hyperthyroidism. For this reason the distinction is often drawn between toxic and non-toxic adenoma, the idea being that in the former the symptoms of thyrotoxicosis are due to hyperfunctioning on the part of the adenoma. There is no satisfactory pathological evidence in support of this idea. As Graham remarks, there are no anatomical, histological, chemical, or pathological features of adenomata which could form a basis of distinction

between toxic and non-toxic goitre. Exophthalmic goitre and toxic adenoma are terms which may be applied to the clinical condition of the patient, but not to the pathological condition of the thyroid. The point is often made that in the toxic adenoma the adenoma is present for a number of years before the appearance of symptoms of hyperthyroidism, and this is used as a means of distinguishing it from Graves' disease in which the symptoms develop at the same time or shortly after the appearance of the goitre. The difference, however, is one of degree rather than kind. The cases regarded as Graves' disease are acute and severe, whilst in the toxic adenomas the thyrotoxicosis and the underlying hyperplasias are mild in degree and therefore later in developing. The explanation of the hyperthyroidism is to be sought not in the adenoma but in the surrounding gland which may or may not show the hyperplastic process originally responsible for the formation of the adenoma.

The more one studies the problem of goitre, the more is one convinced of the mistake of separating toxic adenoma from exophthalmic goitre. Both should be included under the heading of Graves' disease. Atypical cases of exophthalmic goitre may show all the supposed clinical phenomena of toxie adenoma, but the presence of a diffuse goitre and the absence of adenomata compel a diagnosis of exophthalmic goitre. On the other hand there may be well marked adenomata with a full blown picture of exophthalmic goitre. An adenoma may be hyperplastic and be

Fig. 108.—Nodular goitre. Multiple colloid nodules and one dense fœtal adenoma.

surrounded by a colloid gland, or an adenoma may be of the colloid type but be surrounded by a hyperplastic gland. There is, in short, no reason to suppose that the adenoma is in the slightest degree responsible for the symptoms of thyrotoxicosis. The adenoma is a mere incident in the course of the pathological process.

Morbid Anatomy.—An adenoma of the thyroid is a localized encapsulated structure which may be quite small or may be as large as a man's fist. It may be single but more often is multiple. Its most striking feature is its encapsulation, and it is this which is mainly responsible for the idea that it is true innocent tumor. The mode in which this encapsulation

occurs has already been described. It sometimes happens that large numbers of small, poorly encapsulated nodules are scattered throughout the gland. This multiple adenomatosis gives rise to some of the largest of all goitres, but it does not appear to differ in its nature from the more usual form.

It is customary to distinguish two varieties of adenoma known as the colloid and the fetal (Fig. 108). There can be little doubt that very many of the nodules commonly regarded as fetal in type are of essentially the same character as the colloid adenomas, as will be seen in the microscopic description. In addition, however, there is a small group in which a true tumor does arise, possibly from fetal cell rests.

Of all the forms of goitre the adenomatous is the most apt to show degenerative changes. These are especially common in the grey, dense,

Fig. 109.—Nodular goitre (fetal type) with cyst formation.

elastic nodules commonly described as fetal adenomas. The grey surface may be flecked with yellow areas of necrosis. Hemorrhage is common, and may be followed by cyst formation (Fig. 109). The fluid within the cyst is usually brown as the result of the old blood, but it may be clear and shimmering with crystals of cholesterol. In the type regarded as a colloid adenoma, which is similar to a diffuse colloid goitre except that it is encapsulated, cyst formation is common owing to coalescence of adjacent acini with breaking down of the intervening walls. Calcification is a common occurrence in nodular goitre, especially in the fetal variety (Fig. 110).

The *microscopic appearance* is not nearly so distinctive as the gross. In the ordinary colloid form the appearance is the same as that of the involution bodies which appear as the result of administering Lugol's solution in a case of thyroid hyperplasia. The nodule, surrounded by a fibrous capsule, is made up of colloid-filled acini, some of great size, and

lined by a low or flattened epithelium. An occasional spur of epithelium may indicate the presence of a former hyperplasia. In addition there may

Fig. 110.—Commencing calcification in nodular goitre. Numerous fine granules of lime salts are being deposited. × 500.
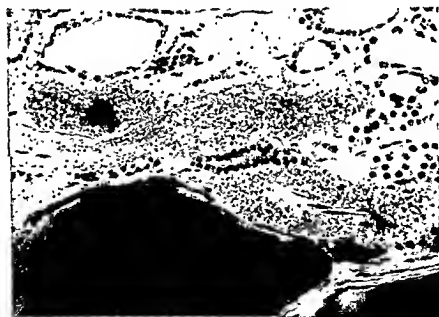
Fig. 111.—Adenoma of thyroid, the upper part shows fetal appearance, the lower part is colloid in type. × 300.

be areas of quite active hyperplasia. The surrounding acini are greatly compressed owing to the pressure exerted by the adenoma. The remainder

of the gland may or may not show areas of hyperplasia. Upon the presence of these areas will depend the toxicity of the goitre. In cases of so-called toxic adenoma there is no pathological evidence that the adenoma itself is in any way responsible for the symptoms of thyrotoxicosis.

In the form usually regarded as the fetal type of adenoma the acini are quite small, and are supposed to be derived from the fetal cell rests in the interacinar parenchyma. Of this there is no convincing evidence. The lining cells are of cubical type, and the majority contain colloid, although some may be empty. It appears to the writer that it is a mistake to draw any fundamental distinction between the colloid and fetal types of adenoma. The one often shades off into the other and in a single section both forms are often represented (Fig. 111).
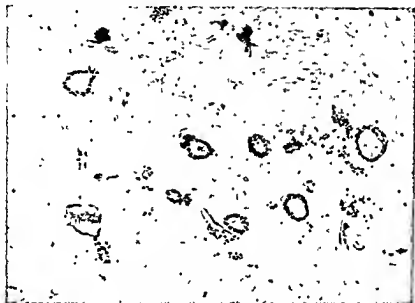
Fig 112.—Thyroid nodule showing characteristic rarefied appearance. Much of the rest of the tissue was in a diffuse colloid condition. × 110.

In the fetal and more rarely in the colloid variety of adenoma the acini may be widely separated by a very peculiar material, the exact nature of which it is difficult to determine (Fig. 112). In most places it is hyaline and structureless, and may so resemble the colloid within the acini in its staining characters that it almost appears as if the colloid had flowed out into the interacinar spaces. More frequently, however, it stains more lightly than the colloid. In other places it contains a few small cells. In still others it appears to be becoming fibrous (Fig. 113). In my own material I have observed that three additional features may be expected in these areas. First, there are often large numbers of dilated thin-walled vessels. Second, hemorrhage is frequent, presumably from these dilated vessels (Fig. 114). The cause of this hemorrhage in an apparently resting gland is also quite obscure. In the hemorrhagic areas the colloid often appears to have flowed from the acini into the intervening stroma, perhaps washed out by the serum of the blood. In one

of my specimens half the adenoma was of a deep red color, owing to the presence of abundant interacinar hemorrhage. The other half was
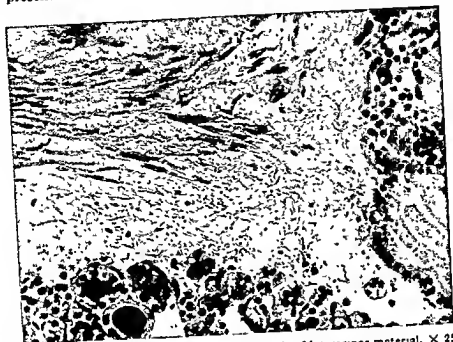
Fig. 113.—Nodular goitre with progressive fibrosis of interacinar material. × 250.
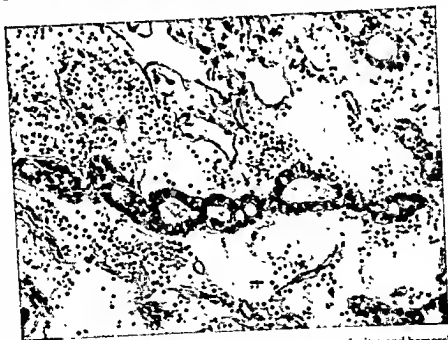
Fig. 114.—Nodular goitre showing epithelial budding, great vascularity, and hemorrhage. × 175.

quite pale. In the hemorrhagic part the space between the acini was flooded with colloid, whereas in the pale part the colloid was strictly

confined to the acini. Thirdly, **many of the acini show active budding.**
There may be three or four buds arising from one acinus, some of them

Fig. 115.—Rarefied part of adenoma; acini widely separated, great vascularity, marked budding with the formation of new acini. × 400.

Fig 116.—Lipoid-filled cells in a thyroid adenoma. × 200.

merely solid masses of cells growing out from the wall, others with a
definite lumen representing a new-formed acinus (Fig. 115). These new
formations are quite different from the buds of epithelial hyperplasia

which project into the lumen of the acini, and which are never seen in these rarefied areas.

We have already seen that in the diffuse colloid form of thyroid all of the above features may be present. The budding of the acini already alluded to in the diffuse form can be observed to great advantage in the nodular variety. This may represent an attempt at the formation of new acini. If this is so it is evident that the new acini are being formed from already existent adult acini. It is commonly held that any new formation in an adenoma is from the cell rests of Wölfler, the interacinar parenchyma. In my own material there appears to be much more evidence of formation from pre-existing acini than from these supposed embryonic cell rests. It will be recalled that after a certain period of fetal develop-

Fig. 117.—Hurthle-cell tumor. Normal thyroid tissue to right. × 120.

ment all the new acini are formed as the result of budding from acini which are already formed.

In nodular goitre one sometimes sees acini which contain large numbers of large clear cells with a small nucleus and vacuolated or foamy cytoplasm (Fig. 116). Sometimes these acini are the seat of hemorrhage, but more frequently this is absent. These cells appear to be phagocytic in nature, and the substance which they contain is probably cholesterol ester. It gives a positive reaction with the ordinary stains for lipoid.

Hürthle-cell Tumor.—This is a convenient descriptive term for a certain microscopic picture, although it is doubtful if the name can be fully justified. It is an adenoma the cells of which bear a striking resemblance to those of the liver, for they are large, polyhedral, with abundant strongly acidophilic cytoplasm, and arranged in trabeculae or small acini (Fig. 117). These lesions are usually benign, but may be malignant (adenocarcinoma): in the latter case the cells show the usual malignant characteristics. In 1890 Hürthle described a large acidophilic cell on the outer surface of the walls of the follicles.

and the tumor is supposed to arise from these cells which some authors have suggested to be parathyroid rests, but it is more probable that the acidophilic character of the cells signifies a functional change such as often occurs in the normal thyroid, and that they are not separate anatomical structures. The term *Langhans tumor* (*wuchernde Struma*) occurs frequently in European literature. It is difficult to be certain of the identity of this lesion, but it seems to bear a close resemblance to the H"rthle-cell tumor, although usually markedly invasive.

DIFFUSE GOITRE WITH HYPERPLASIA (Exophthalmic Goitre: Graves' Disease)

This disease is very much commoner in women than in men. It usually commences in early adult life, and the onset may be sudden and acute, or slow and insidious.

The *cause* of the disease is still obscure. Graves' disease is not pure hyperthyroidism, because the clinical picture cannot be duplicated by the administration of thyroid extract. Evidence is accumulating to suggest that stimulation of the thyroid by the pituitary is a primary factor, the pituitary in turn being played on by impulses from the hypothalamus. Signs and symptoms of terror similar to those of Graves' disease are seen in the adreno-sympathetic outbursts which originate in the hypothalamus and may follow encephalitis lethargica. The disease may follow a terrifying experience, and many patients in whom the disease had been held in check by thyroidectomy suffered a relapse as a result of the bombing raids on London. In the experimental animal a clinical picture not unlike that of Graves' disease can be produced by the use of the thyrotropic hormone of the pituitary. In this disease the pituitary-thyroid axis appears to be geared to a higher level.

The four cardinal symptoms are enlargement of the thyroid, exophthalmos, tachycardia, and excitability of the nervous system as evidenced by tremors, etc. In addition the skin is moist and readily becomes flushed, the patient is very excitable and irritable, palpitation, diarrhea, and vomiting may occur, and peculiar eye symptoms are frequent. Loss of weight is a constant feature.

Perhaps the most important change is the enormously increased body metabolism, as indicated by calorimetric observations. It is as if some blast were blowing on the furnace of the body, fanning it into a condition of furious activity. There is no other disease condition in which a comparable increase occurs. As a result of the rapid nitrogen metabolism it is but natural that the patient should waste away as if being burnt up. On the other hand carbohydrate metabolism is so interfered with that the sugar tolerance is lowered, the blood sugar is above normal, and glycosuria is apt to occur. This may be due to the inhibitory influence which the thyroid is known to exert on the pancreas, or possibly to the heightened activity of the sympathetic interfering with the storage of glycogen in the liver.

The course of the disease varies. It may be of an acute and fulminating type, the patient dying of the disease itself, with symptoms of acute hyperthyroidism, cardiac dilatation, wasting, and exhaustion. Such cases accord with the classical picture described by Graves. Other cases pursue a less violent course, and are marked by a series of remissions and exacerbations, the histological counterpart of which is involution and hyperplasia. Finally there are still milder examples of hyperthyroidism which

differ from acute Graves' disease in degree rather than in any essential qualitative manner. In these cases adenomatous nodules are very apt to develop as the result of involution, and such cases have been classed as toxic adenomas by Plummer and his followers. Closer investigation has shown that these cases do not differ from true exophthalmic goitre in any essential detail, clinically, histologically, or in their response to iodine.

The disease is more or less self-limited. The fire burns itself out, the thyroid breaks down under the constant stimulation, degenerative changes follow, and a partial condition of myxedema or thyroid insufficiency may develop. By the time the thyroid has ceased hyperfunction-

Fig. 118.—Exophthalmic goitre. Moderate enlargement of the gland.

Fig. 119.—Thyroid: exophthalmic goitre. The cut surface resembles the pancreas in texture.

ing many of the vital organs, particularly the heart, have been permanently damaged, and the patient is merely a wreck, and a permanent wreck, of her former self.

Morbid Anatomy.—The thyroid is moderately enlarged, seldom to an extreme degree (Fig. 118). In some cases no enlargement can be detected clinically, the thyroid being tucked away behind the trachea. There is therefore, no goitre in the ordinary sense of the word. Such cases are apt to prove very puzzling, and it is only when the basal metabolic rate is taken that the hyperthyroid character of the symptoms can be diagnosed with certainty. In rare cases even at operation no enlargement of the gland is found.

The gross appearance is very characteristic in untreated cases, but this appearance is apt to undergo a marked change as the result of the involution produced by the preoperative use of Lugol's solution. The untreated thyroid is firm in consistence, and of a dense, opaque, meaty or beefy appearance, very different from the translucent look of the colloid gland (Fig. 119). The enlargement is characteristically diffuse, although sometimes more marked on one side than on the other. In those cases which have passed through a series of remissions and exacerbations, adenomata, that is to say involution bodies, may develop with a well marked capsule. Even the typical thyroid of Graves' disease shows a fine lobulation which is quite characteristic, and which at once suggests a resemblance to the cut surface of the pancreas (Fig. 120).

Fig 120.—Diffuse hyperplastic goitre, showing distinct lobulation when viewed under a low magnification. × 16.

In those cases which have received a preliminary course of iodine there is a marked transition toward the colloid type of thyroid, a transition, however, which varies very much in degree in different cases. The gland is now of a much more translucent appearance, but with the naked eye, better with a hand lens, and best of all with a dissecting microscope, small opaque areas can be seen on the cut surface scattered through the translucent colloid. These are areas of hyperplasia which have resisted the involution induced by the iodine.

The microscopic picture is one of diffuse hyperplasia and great glandular activity. The vessels are dilated. The epithelium is tall and columnar, and many of the nuclei display that irregularity in size and abnormal staining qualities which are suggestive of rapid multiplication, a suggestion which is confirmed by the presence of mitotic figures. Two main types of hyperplasia may be observed. In the first and commonest the acini are increased in size but not in number. The increased dimen-

sions of the acinar spaces are not readily evident, because of the great
infolding of the proliferated epithelium which projects into the lumen
in the form of large papillary processes (Fig. 121). It is only when hyper-
plasia is followed by involution and the papillary processes are withdrawn
that the enlarged size of the acini becomes apparent. In the other form
of hyperplasia there are great numbers of small rounded acini lined by
columnar epithelium, but with no infolding and no papillary processes
(Fig. 122). Both types of hyperplasia are often found in the same thyroid.
In both there is a significant change in the nature of the colloid. It is no
longer abundant and dense, but is scanty, thin, and watery, staining very
faintly. The change in the colloid is most noticeable around the margin
of the acinar space where it comes in contact with the epithelium (Fig.

Fig. 121.—Graves' disease showing absorption of colloid in the vicinity of the hyper-
plastic epithelium. × 75.

123). In this region the colloid often presents a markedly vacuolated
appearance, which is apt to be mistaken for an artefact, a shrinkage
produced by the process of fixation. This is no artefact, however, and the
appearance seems to indicate that the colloid, which after all is an emer-
gency ration, is being absorbed and is passing through the epithelial cells.

Even in untreated cases it is seldom that one sees an absolutely uniform
picture of hyperplasia. Here and there may be seen distended acini in
which the colloid is beginning to reaccumulate and the epithelial pro-
jections are being withdrawn. This is infinitely more pronounced in cases
treated with Lugol's solution. In such cases the greater part of the section
may present the appearance of a colloid thyroid with only here and there
small islands of hyperplasia. What it is that governs the distribution of
these islands we do not know. They are not lobular in distribution, for
both colloid and hyperplastic areas are often seen in the same lobule.
Moreover the degree of involution varies greatly in different cases, for in
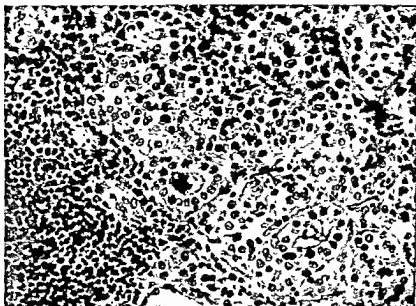
Fig. 122.—Graves' disease showing epithelial hyperplasia and lymphoid hyperplasia × 300.
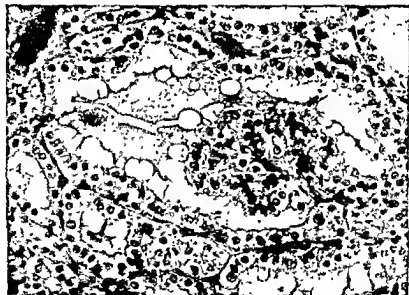
Fig. 123.—Graves' disease showing hyperplasia. The colloid in contact with the epithelium is being absorbed and shows marked vacuolation. × 300.

some the hyperplasia appears to be entirely resistant to the action of the iodine.

Thiouracil, a urea compound which improves the clinical condition to a remarkable degree and reduces the basal metabolic rate, has little

or no effect on the microscopic appearance. The thyroid continues to be hyperplastic, the cells lining the acini are columnar, and the colloid is scanty, thin and vacuolated. It is probable that the thiouracil acts through the anterior pituitary on the thyroid, although it appears also to depress the synthesis of thyroxin.

In addition to the greatly increased vascularity the stroma often shows definite collections of lymphocytes. Nor are they merely collections. They frequently present a definite follicle formation with a center of larger pale cells corresponding to the germinal centers of lymph nodes and other masses of lymphoid tissue (Fig. 124). These lymphoid collections form a very striking feature in many of the cases. Their significance, their real meaning, is at present quite unknown. In my own material they have been much more numerous and more pronounced since the

Fig. 124.—Marked lymph follicle formation as well as epithelial hyperplasia in Graves' disease. × 40.

introduction of the use of Lugol's solution. In a thyroid showing nothing but epithelial hyperplasia these collections may be absent. It is when evidence of involution can be detected that they make their appearance. They are therefore most numerous in those cases which have been treated with iodine. Moreover in myxedema collections of round cells form a striking feature of the microscopic picture. It may be that the appearance of these collections is part of the involutionary process. One is unable to explain this, but on the other hand one is equally unable to explain their presence as part of the process of hyperplasia.

As hyperplasia gives way to involution the stroma of the gland becomes thickened, and large dense strands of fibrous tissue may be seen traversing the section. This may be of the nature of a replacement fibrosis. It hardly seems justifiable to regard it as evidence of a true inflammatory process.

The Relation of the Thyroid to Graves' Disease.—Graves' disease, whether in the form of exophthalmic goitre or the so-called toxic adenoma, is regarded as a manifestation of hyperthyroidism. The very word hyperthyroidism, as Hoover points out, is enough to silence all questions, signifying, as it does, that the symptoms are due to overactivity on the part of the thyroid. The thyroid hyperplasia is supposed to be the anatomical basis of the hyperthyroidism. But we may be allowed to ask if the evidence of this causal relationship is of such a nature that it must inevitably be accepted. The association of the two conditions does not answer the question as to which is the primary. Certain it is that the mere presence of hyperplasia does not necessarily mean that hyperthyroidism is also present. Marine showed long ago that when a large part of the thyroid was removed, the remaining portion showed a picture identical with that of Graves' disease, and yet the animal showed no evidence of hyperthyroidism. Both in animals and man hyperplasia may be present without any symptoms of hyperthyroidism. If the thyroids from a series of routine autopsies are examined, one will be surprised at the frequency with which hyperplasia will be encountered. In Graves' disease the hyperplasia may disappear and the gland revert to a colloid condition, and yet symptoms of hyperthyroidism may persist.

These facts justify us in asking if hyperplasia of the gland is really the cause of the toxic symptoms. Hypertrophy of the left ventricle is associated with arterial hypertension, but the cardiac hypertrophy is the result, not the cause, of the hypertension. The same may be true of Graves' disease. May the condition not be due to a far-reaching disturbance of body metabolism from some unknown cause, as a result of which a demand is made upon the thyroid for additional secretion? At first the stored colloid is used up, and this is succeeded by hyperplasia of the epithelium. If this be true, then the hyperplasia is compensatory and not causal, in which case the prevalent practice of removing a large portion of the struggling gland is hardly likely in the end to prove the best method of treatment.

Changes in Other Organs.—The thymus is usually found to be enlarged at autopsy. The *lymphoid tissue* shows a general hyperplasia, which is seen in the tonsils, the Peyer's patches in the small intestine, the solitary glands in the large intestine, and the lymph follicles in the spleen. The blood may show a relative lymphocytosis. The *heart* may be enlarged and show myocardial degeneration, but there are no specific lesions. There is no such entity as the "thyroid heart." There is fatty degeneration of the *muscles*; the difficulty which the patient has in lifting his foot to a height (quadriceps sign) is due to fatty change in the quadriceps extensor. The *adrenals* may be atrophic. The *bones* often show marked rarefaction and decalcification in the X-ray picture, a change associated with marked increase in the excretion of calcium.

The condition of the *liver in thyroid disease* is now recognized to be of prime importance. Many surgeons believe that deaths occurring in hyperthyroidism are chiefly liver deaths. There is no constant pattern in the liver lesions, but they are essentially congestion and degeneration. Fatty degeneration is extremely frequent. There may be acute necrosis, both focal and central. Subacute toxic atrophy may occur, with the

development of cirrhosis and nodule formation. Liver function tests show a marked degree of functional impairment in a large number of cases of thyroid disease. Boyce in his monograph on "The Role of the Liver in Surgery" likens the *thyroid crisis* or *thyroid storm* to the "liver shock" type of death which sometimes follows surgery of the biliary tract. He suggests that in toxic thyroid disease the over-stimulated metabolism results in combustion of the protective glycogen of the liver beyond the degree of safety. When that point is reached there develops sudden and extreme hyperpyrexia, an almost uncountable pulse, vomiting, diarrhea, and restlessness which may pass into delirium, coma and death.

INFLAMMATION

It is but natural that such a highly specialized gland as the thyroid with so abundant a blood supply should be involved in general inflammatory processes. It is seldom that the inflammation thus induced attains to any marked degree. If, however, general conditions predisposing to thyroid degeneration, such as chronic malnutrition, be present, symptoms of thyroid insufficiency may subsequently develop which may be traced to the previous injury thus received.

A mild form of thyroiditis may be present in many infections, but more especially in acute tonsillitis and acute articular rheumatism. A severe attack of typhoid fever, which leaves its marks on so many tissues, may damage the thyroid to a considerable degree. The gland is often somewhat enlarged and tender in secondary syphilis, so that in some countries this is regarded as an indication of importance.

In exceptional cases suppuration may develop, the gland becomes swollen and inflamed, and an abscess forms. This may discharge into the mediastinum, or into the larynx, trachea, or esophagus. If recovery occurs the usual scarring will result, with frequent deposition of lime salts.

The effect on the thyroid of a general intoxication is always more marked when the gland is already diseased, even though it may be in a quiescent state. Thus in one case of Graves' disease which came under my observation there had been no symptoms of hyperthyroidism for four years, but an attack of epidemic encephalitis resulted in a return of all the symptoms.

Riedel's Struma.—In *1896 Riedel described a "chronic inflammation* of the thyroid leading to the formation of an iron-hard tumor," the condition subsequently known as Riedel's struma. The gland enlarges rapidly and is found at operation to present a remarkable appearance. The enlargement is uniform and smooth, the color whitish, the limits are poorly defined as the gland appears to merge with the surrounding tissues to which it is firmly adherent, and it is of an extraordinarily hard consistence so as fully to deserve the name of iron or woody thyroiditis. In the first case which I encountered I imagined that the specimen must have been preserved in pure formalin before reaching the laboratory.

The microscopic picture varies with the stage of the disease. In the early stage lymphocytic infiltration is a marked feature. Later in the disease the lymphocytes are replaced by a peculiarly dense sclerotic tissue, to which the hardness of the gland is due (Fig. 125). The parenchyma degenerates as the fibrous tissue increases. The cells lining the acini

become detached and fuse around drops of colloid, producing an appearance like that of a giant cell, so that the condition may be mistaken for tuberculosis.

It is not tuberculosis, however, but carcinoma with which the disease is most likely to be confused. Areas of irregular cellular hyperplasia as well as the pale germ centers of the lymph follicles may persist surrounded by dense fibrous tissue and giving a picture highly suggestive of carcinoma. As Shaw remarks, the clinician, the surgeon, and the pathologist may all make a wrong diagnosis of cancer, an error shown by the subsequent benign course of the disease.

The principal symptoms are rapid enlargement of the thyroid, local pain and tenderness and marked dyspnea resulting from pressure on the trachea. It is rather remarkable that there is no evidence of disturbance
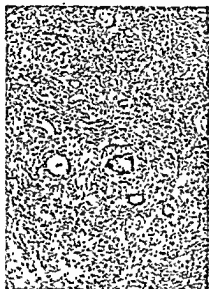
Fig. 125.—Riedel's struma with giant cells. X 80.

Fig. 126.—Hashimoto's disease. X 50.

of thyroid function, either hyperthyroidism or hypothyroidism, in spite of the resemblance which the microscopic picture of the late stage bears to that of myxedema. Although so closely resembling carcinoma it differs from it in that it usually occurs under the age of forty, as a rule the gland has not previously been the seat of goitre, and the surface is not nodular as in carcinoma.

The exact nature of the condition is obscure, and the cause is quite unknown. It appears to be a chronic inflammation, although not related to tuberculosis or syphilis. Ewing calls it a benign granuloma of the thyroid.

Hashimoto's Disease.—In 1912 Hashimoto described a rare lesion of the thyroid characterized by a dense diffuse infiltration of lymphocytes between the acini, together with the formation of secondary lymphoid follicles, sometimes of great size. The microscopic picture may resemble

that of a lymph node. For this reason the lesion is known as *struma lymphomatosa* or *lymphadenoid goitre*. An excellent colored picture of the condition will be found in Joll's monograph. The acini of the thyroid are very largely replaced by the lymphoid tissue (Fig. 126). Fibrosis is also present, but is not a marked feature. The thyroid becomes diffusely enlarged, and is firm or hard. The basal metabolic rate tends to be below normal. It is at once evident that the condition resembles Riedel's struma, and some authorities regard it as an early stage of the latter lesion. The following differences suggest, however, that the two conditions are distinct: (1) Hashimoto's disease is practically confined to women, only one case having been described in a man, whereas in Riedel's
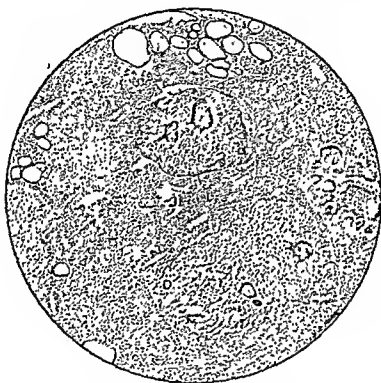
Fig. 127.—Tuberculosis of the thyroid.

struma nearly one-half of the cases are men; (2) Hashimoto's disease is diffuse and bilateral, whereas in Riedel's struma often only one lobe is involved; (3) fibrosis is much more marked in Riedel's struma, and adhesions to the surrounding structures are common, but not in Hashimoto's disease. The nature of the condition is uncertain.

Infectious Granulomata.—Tuberculosis of the thyroid is rare. It usually takes the miliary form, the tubercles being scattered throughout the stroma (Fig. 127). Very rarely large areas of caseation develop. Care must be exercised in distinguishing between true tubercles and the pseudo-tubercles of woody thyroiditis.

Enlargement of the thyroid is common in secondary syphilis. Tertiary lesions such as gummata are very rare.

CARCINOMA

Carcinoma of the thyroid is more common than is usually supposed. It practically always arises in a thyroid, the seat of nodular goitre. It often originates in an adenoma associated with symptoms of thyrotoxicosis. In Simpson's series of 55 cases this association was present in half. It is a rather remarkable fact that although the microscopic picture of Graves' disease is one of wild epithelial proliferation, there appears to be no relation between that disease and carcinoma. Although it may occur as early as puberty, carcinoma of the thyroid is commonly met with in the usual cancer period. It is rather more common in women than in men. It is characterized by a relatively rapid increase in size and hardness in a soft goitre. Such a change should always suggest either carcinoma or hemorrhage into an adenomatous cyst. In one of my cases a large mass
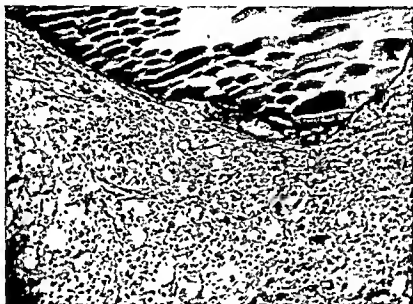
Fig 128.—Carcinoma of the thyroid showing large colloid cyst. Same case as Figs. 129 and 130. × 125.

was formed in the space of three weeks; this proved to be a highly anaplastic cellular type of tumor. Pain and fixation to the surrounding parts are features of importance. Pressure on the trachea often causes dyspnea The condition must be distinguished from woody thyroiditis.

The gross appearance varies considerably. When arising from an adenoma the tumor remains encapsulated for a considerable time, and the pathologist's report may be the first indication to the surgeon that he is dealing with a carcinoma. Sooner or later there is invasion of the capsule and of the surrounding tissue with involvement of the regional lymph nodes. In other cases the tumor is diffuse from the commencement. As a rule the carcinoma is hard, but there may be areas of softening in the center. In the rapidly growing tumor referred to above, the center of the mass was so soft and mushy as to suggest to the operator the likelihood of sarcoma.

The microscopic picture again varies widely (Figs. 128, 129, 130), and many different types have been described. The tumor may be adenocar-
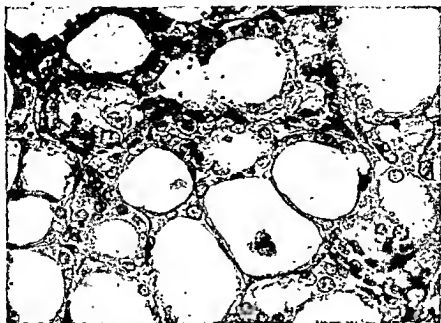
Fig. 129.—Carcinoma of the thyroid showing almost normal thyroid structure. Same case as Fig. 130. × 400.
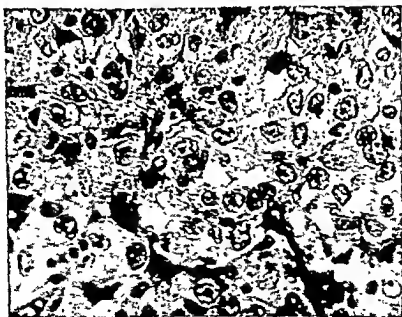
Fig. 130.—Carcinoma of the thyroid showing complete disorder of the normal cellular arrangement. × 500.

cinoma, papillary adenocarcinoma (Fig. 131), carcinoma simplex (medullary or scirrhous) or epidermoid. The papillary adenocarcinoma has a

tendency to spread to the regional lymph nodes, but it is of low malignancy and at the same time curiously radiosensitive, so that enlargement of the cervical nodes is no criterion of malignancy; radical removal and
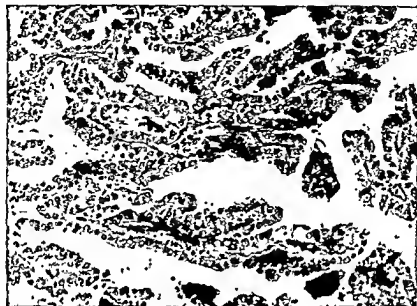
Fig. 131.—Papillary adenocarcinoma of thyroid. × 175.
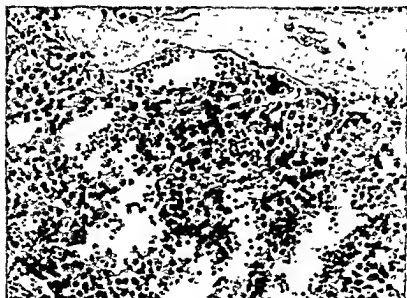
Fig. 132.—Carcinoma of thyroid with mass of tumor cells lying in lumen of vein. × 275.

radiation give good results. The non-papillary adenocarcinomas are much less radiosensitive. They tend to invade the blood stream early though the lymph stream late, so that the prognosis is not good. The carcinoma

may be of an anaplastic small-celled type, rapidly growing and quite hopeless. Epidermoid carcinoma is very uncommon. Not only do different tumors differ from one another, but different parts of the same tumor may show widely varying structure. In one of my cases one part showed a picture of adenocarcinoma, another a picture of medullary cancer, a third ordinary epithelial hyperplasia, and a fourth colloid goitre. An examination only of the last part would lead one to think that the goitre was non-malignant in structure although at the same time it might give rise to numerous metastases. One of the most important features, as Graham has pointed out, is the marked tendency to invade the veins. This is a very valuable point in the diagnosis of those tumors which resemble more or less the structure of normal thyroid tissue. The tumor cells are not separated from the vascular endothelium by a connective tissue, and masses of tumor cells can often be found lying within the thin-walled vessels (Fig. 132). Spread by the blood stream to distant organs is therefore common, and the tumor may grow along the innominate vein and the vena cava as far as the right auricle.

The question of *metastases* is of peculiar interest. Secondary tumors are most common in the lungs, and then in the bones. In my experience secondaries in the bones are not nearly so common as the books would have one believe. The bone most frequently involved is the cranium. A secondary carcinoma in the skull should suggest an examination of the thyroid. A metastatic tumor from the thyroid often shows a remarkable degree of differentiation, so that it may closely resemble normal thyroid tissue. These tumors can produce thyroxin, as is shown by those cases on record in which a thyroidectomy has been done, but myxedema has not developed until some distant metastasis has also been removed under the impression that it was primary tumor.

In conclusion it should be emphasized that the microscopic diagnosis of carcinoma of the thyroid is often very difficult, and that the histological picture is not reliable. Of particular value is evidence of the invasion of the veins.

Fig. 133.—Parathyroid adenoma. A, Actual size. B, Microscopic, showing clear cells. × 500.

PARATHYROID TUMORS

Tumors of the parathyroid are of surgical importance not because of their local effects but on account of the hormonal disturbance in the .

bones known as osteitis fibrosa cystica for which they are responsible. The calcium removed from the bones may be deposited in the kidney to form a renal calculus. Such a stone may be removed several times and be reformed as often before the correct diagnosis is made and the parathyroid tumor removed. As the biochemical aspects of the subject are considered in connection with osteitis fibrosa cystica (page 717), only the morbid anatomy of the tumor will be described here.

The tumor is a benign adenoma, although invasive carcinomas have been described. It may be single or multiple. Usually it is well encapsulated (Fig. 133A). It may be large enough to be palpated, but often this is not possible either because of the small size of the tumor, or because of its position. It may be embedded in the thyroid gland, or may be situated in the upper mediastinum behind the sternum. Occasionally in place of an adenoma there is a diffuse hyperplasia affecting all four parathyroids. *Microscopically* the adenoma usually consists of masses or chords of large clear cells ("water-clear cells") which may have a ballooned appearance owing to the abundant glycogen which they contain (Fig. 133B). There may be many of the oxyphil cells which are present in the normal parathyroid.

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LIPS, MOUTH, AND TONGUE

THE LIPS

The common pathological appearances in the lips are (1) fissures or cracks, (2) scars, (3) an indurated nodule which may be ulcerated.

Fissures.—The somewhat painful condition called "cracked lip" is of common occurrence in young people in cold weather.

Any other fissure is most probably *syphilitic*. A syphilitic fissure may be distinguished from the preceding condition by the red infiltration which surrounds it, and by the fact that when the lip is everted a mucous patch may be found on the inside corresponding to the fissure. Such fissures are commonest at the angles of the mouth.

Scars.—The presence of white, stellate scars at the angles of the mouth is strong presumptive evidence of a previous attack of syphilis, and especially of congenital syphilis. The scars represent the site of healed fissures.

An *indurated nodule*, which may or may not be ulcerated, is probably either an epidermoid carcinoma or a primary chancre. If on the lower lip the condition is likely to be epidermoid carcinoma, although a chancre may also occur there. If on the upper lip it is almost certain to be syphilitic.

Epidermoid Carcinoma.—Epithelioma of the lip (Fig. 134) is the commonest form of malignant disease of the face, and accounts for 2 per cent of all deaths from cancer. It is at least 20 times commoner in the lower than in the upper lip. Moreover it is much more frequent in men than in women; most of the figures attribute only from 2 to 5 per cent of the cases to women. It has long been taught that the habit of pipe-smoking is sufficient to explain this difference, but Broders has shown that this belief is without foundation, for he found relatively little difference in the frequency in smokers and non-smokers.

The general rule that cancer does not originate in an absolutely healthy tissue holds true in the case of the lip, for it is frequent to find an antecedent history of a cracked or fissured lip, an abrasion due to the chronic irritation produced by a jagged tooth, or even the trauma associated with playing the flute or the bugle. Any lesion which breaks the protective covering of epithelium, such, for instance, as a crack, or a patch of seborrhea or leukoplakia, may be the precursor of epithelioma. In several of our cases a cigarette burn was the starting point of the lesion.

The disease begins as a flat nodule or an indurated crack at the junction of the skin and mucous membrane. If the growth extends towards the surface an ulcerated, fungating, warty mass is formed. If towards the deeper structures an indurated nodule is the result, which only becomes ulcerated later. The ulcer presents the hard, raised edges char-

acteristic of malignancy. As the ulcer spreads it may destroy the lip and the tissues covering the chin, and may finally involve the mandible. The disease, if not treated, usually terminates fatally in from two to five years. Removal of the tumor and of the infected glands results in cure in 70 per cent of cases so that this is a particularly favorable form of
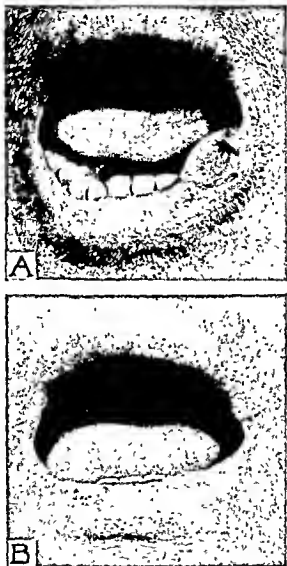
Fig. 134.—Epidermoid carcinoma of lip, A, before, and B, after treatment with radium. (Kindness of Dr. Gordon Richards.)

cancer to treat. One reason for this is that a large proportion of the cases are of relatively low grade and do not involve the lymph nodes for a considerable time. This is in striking contrast to what is found in cancer of the tongue.

Like epithelioma in other positions the disease is locally malignant, involving the neighboring lymph nodes, but seldom setting up metastases

in the internal organs. The lymphatics from the upper lip to the lateral part of the lower lip drain into the submaxillary nodes, those from the central part of the lower lip into the submental glands. From both of these nodes tumor cells may pass to the deep superior cervical nodes. Even when the floor of the mouth is extensively invaded by the growth it is very seldom that the salivary glands are the seat of metastases. Glandular involvement may be noted within three months, but quite frequently it is delayed for nine or twelve months. It is well to bear two points in mind: (1) the nodes may be involved, but may show no enlargement; (2) the enlargement may be inflammatory and not malignant in nature. I have seen two cases in which the bone of the lower jaw was involved at some distance from the growth of the lip. This was probably due to spread along the perineural lymphatics.

Fig. 135.—Angioma of upper lip.

Chancre.—Extragenital infection of the lip, usually the upper one, may occur in three ways. (1) A person with active syphilis of the mouth may infect another by kissing. (2) An infant may be suckled by a syphilitic wet nurse. (3) The spirochete may be conveyed through the use of infected utensils.

The lesion begins as an indurated nodule, which may ulcerate and present the usual appearances of a hard sore. The submental and submaxillary glands on both sides soon become enlarged and hard. Healing takes place at the end of a month or six weeks. In distinguishing the condition from cancer the demonstration of the Spirochaeta pallida in the discharge from the sore, and the rapid response to antisyphilitic treatment, are of great value.

Other rarer conditions found in the lip are angioma (Fig. 135) and lymphangioma. An *angioma* forms a localized swelling the surface of which presents a tell-tale bluish tinge. A *lymphangioma* gives rise to a more diffuse enlargement of the lip, to which the term macrocheilia is applied. Both of these conditions are congenital, and usually occur in children.

THE MOUTH AND PHARYNX

Stomatitis.—Inflammation of the buccal mucous membrane may be catarrhal, ulcerative, or gangrenous.

The *catarrhal* form is common in poorly-nourished children. There is general redness and swelling of the mucosa, or there may be localized

grey patches with a sharply defined margin which are often very tender. In the *ulcerative* variety there may be small superficial ulcers, occurring especially at the angles of the mouth, or the destruction may be more general and deep. The *gangrenous* form, also called cancrum oris or noma, starts as a black spot, which soon spreads so as to involve a large area, and is accompanied by severe constitutional disturbance.

The different varieties of stomatitis are all dependent on conditions of lowered vitality, so that treatment must be general as well as local.

Carcinoma of the Mouth and Pharynx.—The malignant epithelial tumors of the mouth and pharynx form a group of great interest to the pathologist and radiotherapeutist. They differ in structure, in malignancy, and in radiosensitivity depending on whether they lie in front of the anterior pillars of the fauces or behind that line, just as the tumors of the anterior two-thirds of the tongue

differ from those in the posterior third. The members of the posterior group are more anaplastic, more highly malignant, and more radiosensitive. The tumors are epidermoid carcinomas, but two subclasses have been distinguished in the posterior group. These are known as transitional cell carcinoma and lymphoepithelioma; they occur principally in the pharynx, and are characterized by a marked degree of radiosensitivity, but it must be noted that pharyngeal tumors in general are more radiosensitive than those of the mouth, intrinsic larynx, or esophagus. The *transitional cell carcinomas* form about 10 per cent of the malignant tumors of the mouth and pharynx. The word transitional means intermediate *between the squamous and simple* types of epithelium. It has been

Fig. 136.—Transitional cell carcinoma. × 500.

claimed that the epithelium covering the lymphoid tissue in the pharynx, especially in the tonsil and base of tongue, is modified by close association with lymphocytes, and give rise to a specific type of carcinoma which has been called by Regaud *lympho-epithelioma*. This may be regarded as a subvariety of transitional cell carcinoma. It is characterized histologically by a great admixture of lymphocytes, and as the epithelial cells are round and undifferentiated it is evident that the distinction between such a tumor and lymphosarcoma is difficult and in some cases impossible.

Both the transitional cell carcinoma and the lympho-epithelioma present important differences from the squamous cell carcinoma which is characteristic of the skin and of many parts of the mouth. Histologically they do not form squamous cells, cell nests or cornified material. They are

composed of sheets of small round or polyhedral cells, with a large hyperchromatic nucleus which occupies most of the cell (Fig. 136). The cells vary much in size, and mitoses are numerous. The tumors arise in the base of the tongue, pyriform sinus, tonsil, pharyngeal wall, and nasal mucosa. The primary lesion is often characteristically hidden, and may remain undetected for a time even though specially looked for. The only clinical evidence may be fixation of the mucous membrane overlying the tumor. In many cases it probably arises from the ducts of glands opening on the surface rather than from the surface mucosa. All that may be seen is a finely granular surface or slight erosion. Such a minor lesion in a recess like the sinus pyriformis is very readily overlooked. The spread of the growth is deep rather than superficial. The base of the skull may be penetrated, and pain in the ear is common.

Although the primary lesion is often so difficult to detect, the involvement of the regional lymph nodes in the neck is very striking. There may be a large glandular mass in the neck with no detectable lesion in the mouth or throat, so that diagnosis of lymphosarcoma may be made, a mistake which may not be corrected even when a gland is removed for microscopic examination. Distant lymph nodes (retroperitoneal, etc.) may also be involved, still further suggesting a relationship with lymphosarcoma. In marked contrast to what occurs in squamous carcinoma in the mouth or elsewhere, visceral metastases (liver, bones, etc.) are very common.

The radiosensitivity of the transitional cell tumors (including lymphoepithelioma) is very striking, and again contrasts with the ordinary squamous cell form of epidermoid cancer. Indeed it is this feature which first drew attention to the group, and led to renewed studies in histogenesis and in the histological varieties of epithelium. It is in the massive secondary growths in the neck that the effect of radiation is most readily observed. Here again there is apt to be confusion with the lymphosarcomas.

In conclusion it may be pointed out that much of what has been said under this heading may be summed up by saying that in the mouth and pharynx there occurs a group of highly anaplastic radiosensitive epidermoid carcinomas characterized by the inconspicuous character of the primary lesion, the massive involvement of regional and distant lymph nodes, and the formation of visceral metastases. The more anaplastic the carcinoma, the greater becomes the difficulty of distinguishing it from lymphosarcoma.

The mouth is a region where precancerous lesions may be observed to precede the onset of carcinoma. Leukoplakia and the irritation of a badly fitting dental plate deserve special mention. Chewing tobacco may produce leukoplakia which leads to cancer. Friedell and Rosenthal present 8 cases in which carcinoma developed at the point at which the quid was held.

Degenerative mucous membrane changes are found in the majority of mouth cancers. These are usually the result of a combination of avitaminosis with various forms of chronic irritation, e. g., tobacco, syphilis, and sepsis (Martin and Koop). Avitaminosis B is the most frequent form of deficiency, and probably the most important from the standpoint of

carcinogenesis. The lack is aggravated by the restricted diet necessitated by the painful mouth lesion. Vitamin therapy must therefore be considered in the treatment of oral cancer. It is quite probable that avitaminosis lesions are not confined to the mouth, but involve the entire gastrointestinal tract. If so they may play a part in gastric and intestinal cancer.

Post-cricoid carcinoma deserves separate consideration. The post-cricoid region of the pharynx, situated behind the larynx, forms part of the hypopharynx, *i. e.*, the region which lies below the epiglottis. The remainder of the hypopharynx is constituted by the sinus pyriformis. Post-cricoid carcinoma presents some curious features. Carcinoma of the mouth, oropharynx, sinus pyriformis and esophagus is very much commoner in men; it is a male disease. Post-cricoid carcinoma, on the other hand, is a female disease, 80 per cent or more of the cases occurring in women. The probable reason for this is that the condition known as anemia with dysphagia (Plummer-Vinson syndrome), which is much commoner in women, is a precancerous condition. Owing largely to an iron deficiency in the diet the mucous membrane of the pharynx and hypopharynx becomes dry, cracked and finally inflamed, a condition which evidently predisposes to the development of carcinoma. Histologically the tumor is a squamous cell carcinoma, whereas carcinoma of the sinus pyriformis is usually of the transitional cell type. Pharyngeal cancer commencing in the sinus pyriformis or around the upper aperture of the larynx first produces hoarseness and difficulty in phonation. Post-cricoid carcinoma, on the other hand, causes difficulty in swallowing. It usually commences on the pharyngeal mucosa covering the back of the cricoid cartilage (anterior wall of hypopharynx), and spreads in tubular form around the lowest part of the pharynx, causing marked stenosis.

Plasmacytoma.—The ordinary plasma cell tumor is the myeloma of bone marrow, but extramedullary plasma cell tumors occasionally occur, and one of the principal sites is the nasopharynx. The tumor shows a diffuse arrangement of typical plasma cells, and is usually mistaken for a lymphosarcoma, but it is usually benign, although sometimes showing a tendency to invasion. The plasmacytoma appears to be more of a granuloma than a neoplasm, and the prognosis is correspondingly good.

Mixed Tumors of the Palate.—The soft palate is occasionally the seat of a benign growth of the same nature as the mixed tumors of the salivary glands. The nature of these tumors has already been discussed in Chapter X.

Ulcer of the Palate.—The usual cause of ulceration of the palate is tertiary syphilis. Much more rarely it may be due to cancer or tuberculosis.

The *syphilitic* ulcer commences as a gumma. Necrosis occurs, with the separation of a slough, and the ulcer finally perforates the palate, leaving a punched-out opening of varying size through which food regurgitates into the nose.

Retropharyngeal Abscess.—This is a condition in which pus is formed in the loose tissue between the posterior wall of the pharynx and the vertebral column. It may be acute or chronic. The acute form occurs in children at the end of a debilitating illness. In addition to marked constitutional symptoms, there is rigidity of the neck, great pain on swallowing, loss of voice, and a tense swelling can be felt—seldom seen on account of inability to open the mouth—on the posterior wall of the

pharynx. A lateral roentgenogram will show great widening of the retro-pharyngeal space in children. Prompt incision is indicated.

The *chronic* form is usually the result of tuberculous disease of the cervical vertebrae.

Ludwig's Angina.—This fortunately rare condition is a diffuse strep-tococcal cellulitis involving the structures at the back of the throat, the tongue, and the neck. The inflammation is intense, and usually proves fatal in a few days.

THE TONSILS

The tonsils may be red and inflamed as the result of tonsillitis, Vin-cent's angina, diphtheria, scarlet fever, and syphilis.

Acute Tonsillitis.—Two forms may be distinguished, the follicular and the parenchymatous.

In the *follicular* variety the tonsils are swollen and red, and the sur-face is dotted with yellowish-white flecks, which are plugs of leucocytes and desquamated epithelial cells projecting from the mouths of the crypts. They can usually be readily wiped off, thus differing from the condition in diphtheria. The inflammation is confined to the lymphoid follicles surrounding the crypts of the gland.

In the *parenchymatous* form or quinsy the inflammation is more general, involving the substance of the tonsils and spreading to the sur-rounding tissues. The constitutional symptoms are much more severe, and the condition usually goes on to suppuration. The inflammation is often more marked on one side, the uvula is deviated to the opposite side, and the presence of pus is indicated by great swelling of the peritonsillar tissue of the anterior pillars of the fauces. The lymphatic glands of the neck are enlarged and tender.

Diphtheria.—On the inflamed tonsil there is a single grey patch, as contrasted with the multiple patches of tonsillitis. It is rather firmly ad-herent, and when removed leaves a red raw surface. A similar patch on the soft palate is pathognomonic. The presence of albuminuria and the absence of knee jerks may help in diagnosis. A bacteriological exam-ination for the Klebs-Löffler bacillus must always be made, but in a sus-picious case the administration of antitoxin should never be withheld until the report of such an examination is received.

Vincent's Angina.—In this condition a grey membrane is present on the tonsil which may readily be mistaken for diphtheria. Somewhat character-istic is the undue amount of destruction, quite a large cavity being often seen when the slough is removed. The secretion contains two kinds of organisms, a long fusiform bacillus with pointed ends, and a delicate spirochete which stains very faintly with the ordinary aniline dyes. When a swab is taken for diagnostic purposes it should be smeared at once on a glass slide, for the diagnosis is made by smear and not by culture, seeing that the organisms do not grow on the ordinary media.

Scarlet Fever.—The tonsil is red and swollen, and may occasionally present yellow muco-purulent patches. The bright diffuse red color of the throat and soft palate, the strawberry tongue, and the skin rash are points of diagnostic importance.

Syphilis.—Early in the secondary stage of syphilis the mouth presents

lesions, which are characteristically bilateral. The tonsils are red and inflamed, and on the surface there are irregular greyish-white patches often likened to snail-tracks. Superficial ulcers may be present. These lesions are not confined to the tonsils, but occur on the fauces, soft palate, and other parts of the buccal mucous membrane.

In the *tertiary* stage deep, punched-out ulcers may be present on the tonsils, fauces, or palate, the result of the breaking down of a gumma.

A *primary* chancre may occasionally be met with on the fauces or tonsils. It is apt to be mistaken for an epithelioma.

Tumors.—A variety of tumors may occur in the tonsil. Epidermoid *carcinoma* may grow from the stratified epithelium which covers the surface. This may be of the squamous cell type. (epithelioma), transitional cell carcinoma or lympho-epithelioma. *Lymphosarcoma* may commence in the tonsil. At first it is unilateral, but becomes bilateral later; the cervical lymph nodes are enlarged. *Plasmacytoma* (plasma cell tumor) is very rare, but of importance in that it is benign and apt to be mistaken for lymphosarcoma; it is composed entirely of plasma cells.

THE TONGUE

Acute Glossitis.—Acute inflammation of the tongue is not common although the reverse might be expected. It may result from a septic wound or from the sting of an insect. Sometimes there is no obvious cause. The tongue rapidly becomes markedly swollen, and may threaten to suffocate the patient. Suppuration may develop, demanding free incision.

Leukoplakia.—This may be described as a chronic superficial glossitis which occurs in middle life as the result of a variety of irritants. Of these syphilis, bad teeth, poorly fitting dentures, excessive smoking, and the use of strong spirits and spices are probably the most important. There is proliferation and heaping up of the cornified epithelium, with the formation of milk-white patches which may be lozenge-shaped so as to give the tongue a mosaic-like appearance. The tongue may look as if it had been smeared with white paint. The condition is confined to the anterior two-thirds of the tongue, commencing at the edges and spreading on to the dorsum. The surface may become fissured and cracked owing to contraction of the underlying tissue caused by the chronic inflammation. In the course of time atrophy tends to succeed hypertrophy, the thickened papillae disappear, the white membrane is worn off, and the surface becomes smooth and red. Microscopically the epidermis is greatly thickened and shows excessive cornification, whilst the underlying tissue is infiltrated with chronic inflammatory *cells* of the small round type, to be replaced later by fibrous tissue.

The great practical importance of leukoplakia is the danger of it developing into carcinoma. Although most cases remain benign it forms a constant menace, and *forms one* of the best examples of a precancerous condition. This is true of leukoplakia of the mouth also. Of 566 cases of leukoplakia buccalis (including the tongue) recorded by Mantilla, 32 per cent developed carcinoma.

Syphilis.—Syphilis of the tongue is common. The lesion may be of the primary, secondary or tertiary type.

The *primary lesion* is an extragenital chancre, and naturally occurs

at the tip. It presents the usual appearance of a hard sore and the Spiro-chaeta pallida can be seen in the discharge with dark-field illumination. Great care must be exercised in *not* confusing these with the other spiro-chetes of the mouth, for it is easy to make a serious mistake. The regional lymph nodes in the floor of the mouth are very greatly enlarged and hard.

The *secondary lesions* are mucous patches which are usually present on the dorsum and sides of the tongue. They present a serpiginous out-line, and numerous spirochetes are present in the discharge.

The *tertiary lesion* may take three forms: (1) leukoplakia, (2) sclero-sing glossitis, and (3) gumma. Leukoplakia of the tongue has already been described. *Sclerosing glossitis* is often associated with leukoplakia. The lesion is similar to that which occurs in the testicle. There is cellular infiltration, followed later by fibrosis. The tongue becomes sclerosed and atrophied, the surface is wrinkled and fissured, or smooth and glazed. *Gumma* is a common lesion of the tongue. It usually forms a single deeply placed nodule of considerable size situated in the center of the tongue close to the middle line. Necrosis occurs, the surface becomes ulcerated, and a characteristic punched-out ulcer with wash-leather base is formed. A syphilitic ulcer may closely resemble a carcinomatous one. Much more important from the surgical standpoint, however, is the fact that in the tongue syphilis is frequently a precancerous lesion (see below).

Carcinoma.—Carcinoma of the tongue is a common lesion. The usual age period is between 45 and 60, but it may occur much earlier. It is a disease of the male, about 90 per cent of the cases being in men. This is usually explained by the fact that such predisposing factors as syphilis and pipe-smoking are commoner in men, but it is probable that the gen-eral tendency of the male alimentary canal to carcinoma (with the excep-tion of the post-cricoid region of the hypopharynx) in comparison with that of the female, is a factor of at least equal importance.

The early diagnosis of cancer of the tongue is a matter of vital impor-tance. Here time must be measured in days, whereas in the case of cancer of the lip it may be measured in weeks or even months. The tumor cells quickly spread from the primary lesion along lymph channels, so as to involve the deeper tissues and near and distant lymph nodes. This rapid spread is due partly to the very rich lymphatic drainage of the tongue, partly to its almost constant muscular movements which tend to dis-seminate the tumor cells. A vivid picture of the end stage, emphasizing the importance of early diagnosis, is drawn by my former colleague, Dr. A. W. S. Hay, in the following words: "Of all the painful deaths by which men leave this world there are few more miserable and agonizing than that which results from carcinoma of the tongue. From the beginning to the dreadful end one distressing feature follows another in rapid suc-cession. Pain is followed by the unspeakably vile fetor of ulcerating infected carcinoma, by the dribbling of foul saliva, and then slow starva-tion day by day until the final climax is reached in a gush of blood or some equally terrible catastrophe."

Precancerous lesions, or, more properly speaking, predisposing factors, play a part of great importance. The chief of these are leukoplakia, syphilis, and the irritation of bad teeth or a badly fitting denture. Heavy pipe-smoking must also be mentioned, but it is more difficult to assess

its exact importance. The tongue is one of the very few regions where there is any relation between syphilis and carcinoma. For this reason a positive Wassermann reaction in a case of ulcer of the tongue must never be taken to exclude cancer, and should be followed up by a biopsy. Bloodgood found that in 160 cases of cancer of the tongue there was a long-standing history of leukoplakia in 41. One of the cracks and fissures which are so characteristic of chronic glossitis is a frequent starting point for carcinoma. Fitzwilliams in his valuable monograph on the tongue remarks that the sore made by a sharp tooth in the leukoplakic tongue of an old man is apt to become malignant in the course of a few months.

The *site of election* is on the anterior two-thirds of the tongue at or near the edge. It rarely affects the tip or the centre, unless it arises in a gummatous ulcer in the latter region.

The *gross appearance* varies. When first seen the lesion may take one of three forms: (1) a hard-edged ulcer, (2) a warty growth, (3) an indurated plaque. The first is much the commonest. The ulcer, situated
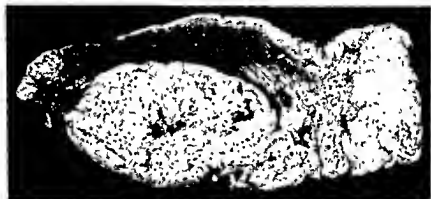
Fig. 137.—Carcinoma of the tongue. To the right of the specimen there is a downgrowth of epithelium. The tumor has extended to the left so as to form a large mass in the muscle of the tongue.

near the edge of the tongue, is characteristically hard, the base is indurated, and the edges are raised and everted. Although the ulcer may be shallow, the carcinomatous tissue will be found to extend much more deeply, for the growth is markedly invasive (Fig. 137). This point must be borne in mind if local removal is contemplated. Sometimes no lesion is visible, but a marked induration can be felt. The warty form is usually superimposed on a previous leukoplakia. The indurated plaque on the surface is a comparatively rare variety. With the progress of the disease the tongue becomes eaten away, the growth is necrotic and heavily infected, and severe pain is a prominent feature.

The *microscopic appearance* depends largely on which part of the tongue is affected. The anterior two-thirds of the tongue is covered by thick, stratified, cornified epithelium with numerous papillae; the submucosa is sparse and there are no racemose glands. In the posterior third there is little or no cornification; there are abundant racemose glands (which are apt to be mistaken for carcinoma), and numerous collections of lymphocytes close to the basal layer of cells. As might therefore be

expected, tumors of the anterior two-thirds are cornifying, epidermoid carcinomas with cell-nest formation. The degree of differentiation, however, will depend on the grade of the tumor, and cancer of the tongue is of a much higher grade than cancer of the lip; examples of Grade I are uncommon. Cancer of the posterior third shows a marked lack of differentiation. It may be of the basal cell type, or transitional cell carcinoma or lympho-epithelioma. It is important not to mistake von Ebner's glands for carcinoma; their ducts open on the base of the circumvallate papillae, and they penetrate deep into the muscle in a manner which may suggest malignancy.

Spread is local and to the regional lymph nodes. Reference has already been made to its extreme rapidity. The floor of the mouth and the neighboring structures are invaded and destroyed. The *lymph nodes* are infected by embolic spread, not by permeation, so that the intervening tissue is not involved. The anterior part of the tongue is drained by lymphatics passing through the floor of the mouth to nodes in the submental region. The body of the tongue is drained into the submaxillary group of nodes lying in relation to the submaxillary salivary gland. Some of the nodes may be imbedded in the substance of the latter gland, so that it has to be removed together with the lymph nodes. The posterior third of the tongue drains into the upper deep cervical nodes on *both* sides of the neck. These nodes also receive lymph from the submaxillary and submental groups, so that in the later stages they are infected no matter what the original site of the tumor may be. The involved glands are enlarged and very hard. It must be remembered that the septic infection which invariably occurs in the malignant ulcer may cause a non-malignant enlargement of the lymph nodes under the jaw. In the later stages the glands on both sides of the neck may be the site of metastases.

The average duration of the disease in unoperated-on cases is from 18 months to 2 years. Death is usually due to septic pneumonia. In the early local stage a local operation is sufficient, but the invasive character of the growth must be borne in mind.

Ulcers of the Tongue.—An ulcer on the tongue may be simple (inflammatory), carcinomatous, syphilitic or tuberculous. The malignant and syphilitic varieties have already been considered.

A *simple ulcer* usually occurs at the edge or tip of the tongue, and is the result of some source of irritation within the mouth, such as a jagged tooth or an ill-fitting plate. In the early stage it is shallow and inflamed, but if the irritant is not removed the ulcer becomes chronic in character, with indurated edges and a base often covered with a slough. Such an ulcer may become malignant. Some persons are subject to recurring minute ulcers on the tip and edges of the tongue, which are extremely tender. The cause of these ulcers is not known, but it is probably in the nature of a constitutional disturbance.

A *tuberculous ulcer* of the tongue is secondary to tuberculous disease of the lung. It is a rare condition, although the tongue has such abundant chances of surface infection from the lungs. The ulcer, which is usually situated at the tip of the tongue, presents the oval outline, sinuous edges, pale watery-looking granulations, and absence of induration characteristic of tuberculous ulcers elsewhere.

As regards ulcers tuberculosis chooses the tip, epithelioma the edge, and syphilis the centre, but of course any of the lesions may occur in any part of the tongue.

ULCER OF THE TONGUE

Variety	Site	Character	Remarks
Inflammatory..	Edge or tip.	Shallow and inflamed.	Assoc. with sharp tooth or plate.
Malignant	Edge or center.	Hard. Begins as crack or nodule.	May be assoc. with chronic glossitis. Lymph nodes enlarged.
Syphilitic ..	Dorsum	Serpiginous in outline.	May be primary, secondary, or tertiary.
Tuberculous. .	Tip.	Undermined edge. No induration.	Always secondary.

In addition to carcinoma other tumors may occasionally occur in the tongue. Of these the commonest is angioma, which takes the form of a soft rounded mass with a blue or purple tinge. The condition is congenital. Sarcoma, lymphosarcoma, papilloma, fibroma and lipoma occasionally occur.

Dermoid cysts may occur beneath the tongue. They may project under the chin or into the floor of the mouth. A thyroglossal cyst or tumor may arise in the base of the tongue at the upper end of the thyroglossal duct.

Macroglossia is a diffuse congenital enlargement of the tongue. Fitzwilliams describes the condition as the tongue of an adult protruding from the mouth of an infant. It may take one of two forms: (1) lymphangiomatous, (2) muscular. The first of these is much the commoner; there is marked dilatation of the lymph spaces. The enlargement of the tongue, which is sometimes extreme, may be diffuse or localized. Recurring attacks of glossitis are common, and with each attack the tongue becomes larger and more indurated. The surface becomes ulcerated, the lower lip rolled out, the teeth deformed, and the lower jaw flattened by the pressure. The condition is usually present at birth, and may be associated with cystic hygroma (lymphangioma) of the neck. The muscular form is rare. There is hypertrophy of the muscle of the tongue, often associated with hypertrophy of other parts and with mental deficiency.

Fissured tongue is a very rare congenital anomaly in which the tongue is divided into two halves. It is sometimes hereditary.

Hairy tongue is another rare condition characterized by hypertrophy of the papillae which become covered with a mass of bacteria and fungi and assume a dark color. The dorsum of the tongue appears to have a patch of hairs attached to the center.

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CHAPTER XIII

THE STOMACH AND DUODENUM

PEPTIC ULCER

The ulcers of the stomach and the first part of the duodenum are so essentially similar and are so dependent on the digestive action of the gastric juice for their production that they are conveniently considered together under the heading of peptic ulcer. The stomach and the suprapapillary part of the duodenum have very much in common. Both are developed from the fore-gut and derive their blood supply from the celiac axis. The remainder of the duodenum is formed from the mid-gut and is supplied by the superior mesenteric artery. Most important of all, the first part of the duodenum, being above the entrance of the alkaline bile and pancreatic juice, is exposed like the stomach to the action of the acid gastric juice.

When the clinician speaks of a gastric ulcer he is usually thinking of the ordinary chronic peptic ulcer. A much commoner condition, frequently seen by the pathologist who is on the lookout for it, is the acute ulcer or erosion. This lesion is of interest to the clinician because it is the forerunner of the ordinary chronic ulcer. At the same time it is usually unattended by symptoms, because as a rule it is confined to the mucosa, whereas symptoms of gastro-intestinal disorder, pain in particular, are essentially muscular in origin.

It is not easy to determine the *relative frequency* of chronic gastric ulcer as compared with duodenal ulcer. Surgical statistics are unreliable because they are based on a special type of case, *i. e.*, one requiring operative treatment. In a series of 4,000 autopsies Stewart encountered chronic gastric ulcer in 2.23 per cent of cases and chronic duodenal ulcer in 3.83 per cent. Operating room statistics represent duodenal ulcer as being much more frequent.

Pathogenesis.—An enormous amount has been written on the pathogenesis of peptic ulcer. Ulcers of the stomach and duodenum may be produced in a multitude of ways. So may ulcers of the leg. The mere fact that an ulcer can be produced in the laboratory by some ingenious method such as the injection of adrenalin bears no relation to the causation of the common peptic ulcer of actual practice. At the same time it is most probable that different causes may operate in different cases.

When the problem is reduced to its simplest terms we may say with assurance that the ordinary peptic ulcer is the result of the continued action of the gastric juice on an area of lowered resistance in the stomach wall. This simple statement does not, however, carry us very far, for we are in ignorance of the exciting cause responsible for this area of lowered resistance, nor do we know why in some cases the result is a superficial erosion which quickly heals, whilst in others it is a penetrating

ulcer which refuses to heal. There are two distinct problems in the pathogenesis of peptic ulcer: (1) What is the cause of the necrosis? (2) What is the reason for the persistence of a chronic ulcer?

Necrosis of the mucosa with the formation of an ulcer may be produced in a variety of ways. Any irritant, mechanical, physical or chemical, may give rise to an erosion. Nursing calves which are taken too soon from their mothers and are given coarse food are prone to develop erosions, due, evidently, to the mechanical irritation. In the same way stock animals are liable to suffer from gastric ulcer in the late winter owing to the coarse type of fodder available at that time. It can be shown experimentally that food at an unduly high temperature may produce gastric erosions; these are seen in dogs which are fed on hot gruel. Peptic ulcer is said to be common in cooks, perhaps for a similar reason. The administration of acids, such as acetic acid and vinegar, may produce first an acute gastritis and then an ulcer.

It is possible that in some cases the cause of the focus of lowered resistance is a local hematogenous infection of the mucosa by organisms of low virulence. This is an attractive idea, but the evidence in support of it has never been really convincing.

Atrophic gastritis affecting the antrum is often associated with gastric ulcer. Hebbel, indeed, from examination of a large number of cases, considers it to be an invariable accompaniment. This suggests that the gastritis precedes and is the anatomical basis for the development of ulcer; in other words, that a chronic ulcer does not develop in a healthy mucosa. This does not serve to explain the development of duodenal ulcer.

Within recent years Cushing has revived Rokitansky's idea of the neurogenic origin of peptic ulcer. He points out that certain brain tumors may end with a perforated gastric ulcer, and that the same is sometimes true of operations on the cerebellum and of intracranial injury in the newborn. He suggests the presence of a parasympathetic center in the hypothalamic region from which tracts relay back with cranial-autonomic stations in the midbrain and medulla, of which the vagus nucleus is the most important. Experimental lesions of these tracts from the hypothalamus to the vagal center have been shown to cause gastric erosions, ulcers, and even perforation, probably due to nervous impulses leading to temporary ischemia and finally necrosis of the gastric mucosa. This would agree with the observation that peptic ulcer is frequent in highly-strung persons and those who have been subjected to much worry.

Food deficiency may play a part in some regions. This is suggested by the extreme frequency of duodenal ulcer in Southern India, particularly Travancore (Somervell). In this district food consists of rice and curry, poor in all the vitamins, particularly A and B_2. In some parts of India, such as the Punjab, where the diet is rich and well balanced, peptic ulcer is singularly rare. It is hardly necessary to point out that whilst the facts just stated are doubtless correct, the conclusion suggested may be quite fallacious.

There can be no doubt that the most important factor in producing a peptic ulcer is the acid gastric juice. This will lead to digestion of an already necrotic or devitalized area, and it is possible that it may be responsible for the initial damage, although it seems probable that it

it must be assisted by some other factor. Hyperacidity is always present in the early stages, although it may disappear in old chronic ulcers. The ulcer always occurs in the non-acid-producing part of the stomach, but in immediate juxtaposition to acid-producing mucosa. Peptic ulcer occurs in Meckel's diverticulum if the diverticulum contains gastric mucosa. Stomal ulcer occurs in the jejunum in juxtaposition to acid-producing mucosa. Worry and nervous strain are associated with hyperacidity, perhaps explaining the prevalence of ulcer amongst surgeons. Histamine which stimulates the secretion of acid, can be used to produce ulcers in the experimental animal, and the implantation of the histamine in beeswax greatly facilitates this production owing to the long-continued action secured by this procedure. In severe burns histaminoid substances are produced, and it has been long known that such burns are occasionally accompanied by the formation of acute ulcers in the stomach and particularly in the first part of the duodenum (Curling's ulcer). The subcutaneous injection of posterior pituitary extract produces acute hemorrhagic lesions, whilst repeated injections lead to the formation of chronic ulcers of the peptic ulcer type (Dodds). If the stomach contents are rendered alkaline, injection of pituitary extract fails to produce ulcers. All of these facts point to the paramount importance of gastric acidity in the production and maintenance of peptic ulcer, although they do not prove that some additional factor may not also be operative.

The most striking demonstration of this truth is afforded by the experimental work of Mann. In considering the effect of the acid juice in producing an ulcer we must not overlook the all-important action of the alkaline duodenal juice in preventing the formation of an ulcer and in bringing about the healing of an established ulcer. The duodenal juice is made up of three alkaline components, the duodenal secretions, the bile, and the pancreatic juice. Mann and Williamson transplanted the bile duct and the pancreatic duct into the lower ileum, with the result that a peptic ulcer developed in 10 out of 31 animals; in 5 of these the ulcers were chronic. The site in all cases was the jejunum immediately beyond the line of suture. The ulcers usually developed a month or two after the operation. In another series of cases the duodenum was excised and the upper end of the jejunum was anastomosed to the pylorus. In practically all these animals a chronic peptic ulcer developed just beyond the anastomosis; the gross and microscopic characters of these ulcers were identical with those seen in the chronic peptic ulcer of man.

The *persistence* of an ulcer in a chronic form is more difficult to explain than the initial production of the ulcer. There can be little doubt that the majority of acute ulcers heal quickly and completely. The ulcers which become chronic are confined to the region of the stomach known as the Magenstrasse (see p. 225), in which experimental injuries heal with difficulty, possibly on account of the absence of mucin production which in other parts of the stomach exerts a protective action. The degree of acidity of the gastric juice may also be a factor of importance. Fleming suggests that failure to heal is due to an innate poor blood supply at the usual sites. The areas of mesenteric attachment in the stomach and duodenum are the lesser curve and the posterior wall respectively, and the alimentary tube is less vascular at the point of its mesenteric attach-

ment than elsewhere. Secondary jejunal ulcer may be due to the ischemia produced by tight stitching.

Age and Sex.—It might be thought that there would be little room for difference of opinion regarding such a matter of fact as the age and sex incidence of peptic ulcer. Such is not the case. This difference is dependent on the source of the statistics employed. It is so difficult to avoid using specially selected material, and the use of selected material for determining the general incidence must of necessity be misleading. The surgeon and the pathologist see only a special type of case, the ulcers which refuse to heal and which lead to obstruction. The clinician, on the other hand, whose cases are in no way selected, can never be absolutely certain of his diagnosis even with all the assistance of the radiologist. A patient even with the most convincing history may show no evidence of organic disease when the abdomen is opened.

By considering all the sources of information, however, we are able to form a fair estimate of the relative frequency of peptic ulcer in the two sexes. Not so long ago we were taught that gastric ulcer was essentially a disease of young women, a conclusion based upon purely clinical evidence. We now know that in many of these cases not only was there no gastric ulcer; there was not even a trace of organic disease of the stomach. The stomach is so sensitive an organ, as Moynihan remarks, that it cannot refrain from weeping when its neighbors are in trouble, and its voice may be so loud as to drown that of the others. These others may be the gall bladder, the appendix, and other parts of the alimentary canal. The chronic type of peptic ulcer, whether gastric or duodenal, is undoubtedly more common in men, generally between forty and fifty. The acute ulcer which heals and the acute perforating ulcer are probably more common in young women.

The relative frequency of gastric and duodenal ulcers is another matter regarding which there is difference of opinion. Surgical statistics show that chronic ulcer is much commoner in the duodenum than in the stomach. In the Toronto General Hospital during the past seven years out of 875 cases of chronic ulcer coming to operation, 663 (70 per cent) were in the duodenum and 212 (30 per cent) in the stomach. It must be remembered, however, that the surgeon sees a special class of cases, those in which symptoms of obstruction form a prominent feature. Thus in the autopsy material of the same hospital the incidence of chronic ulcer in these two locations was almost the same, being a trifle more frequent in the stomach than in the duodenum.

There appears to be little room for doubt that peptic ulcer, particularly of the duodenal type, has greatly increased in frequency in recent years. This is well brought out by Wilkie in an analysis of the figures of the Edinburgh Royal Infirmary. In 1906, 24 cases of duodenal ulcer were treated, and there were in addition 22 cases of perforated duodenal ulcer. Twenty years later, in 1926, 236 cases of duodenal ulcer were treated. In view of the number treated in 1926, the number of cases of perforated ulcer might be expected to show a perceptible decrease if the incidence had not really varied. On the contrary, 102 cases of perforated duodenal ulcers were admitted in 1926, more than four times the number of 20 years ago. From these facts we may surely draw the conclusion that

the disease is really on the increase, and is not merely being diagnosed with greater exactness.

Morbid Anatomy.—Acute ulcers or erosions may occur in any portion of the stomach. The chronic peptic ulcer, on the other hand, is curiously localized in its distribution. Over 80 per cent of chronic ulcers occur on the lesser curvature, principally on the posterior wall of the pyloric portion but exclusive of the pyloric canal (about 1 inch in length). This may be compared with the incidence of gastric carcinoma in which from 60 to 80 per cent of the cases occur in the pyloric canal, the figures differing with different authors. The great majority of chronic ulcers are situated on the Magenstrasse or gastric pathway formed by the oblique fibers of the muscular coat, an area in which the mucosa is attached unduly firmly to the underlying tissue and in which no mucin is produced. These factors possibly interfere with the healing of ulcers.
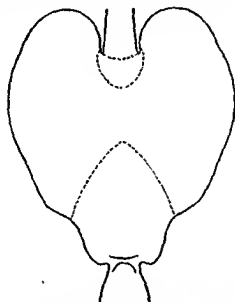
Fig. 138.—The acid-producing area of the stomach lies between the dotted lines.

Peptic ulcer occurs in those portions of the stomach where there are no acid-secreting cells. When the stomach is opened along the greater curvature a V-shaped line can be drawn (the apex pointing to the cardia) which separates the acid-producing fundus region from the non-acid-producing pyloric region (Fig. 138). In the great majority of cases the ulcer occurs just over this line, *i. e.*, on the pyloric side; this localization may be compared with that of secondary jejunal (stomal) ulcer which occurs just on the alkaline side of the opening. Occasionally the ulcer is situated in the fundus; but in these cases if the "acid line" be plotted out it will usually be found that the ulcer falls on the pyloric side of the line. A small proportion of ulcers occur at the cardia, where again there is absence of acid-producing cells. Less than 10 per cent of benign ulcers occur close to the pylorus, whereas over 70 per cent of carcinomas are found in the pyloric area. A prepyloric ulcer should be regarded with great suspicion.

The ulcer is usually single, but in from 5 to 10 per cent of cases it may be multiple (Fig. 139). It is often deep, penetrating the muscular coat to a greater or less depth. It may have a punched-out appearance with

Fig. 139.—Multiple ulcers of the stomach.

abrupt walls, it may be funnel-shaped, or the edges may be terraced (Fig. 140). The steps of the terrace are best marked at the pyloric side of the ulcer, possibly due to the greater traction in that direction, whilst on the cardiac side the wall is steep and abrupt. The edges are raised

Fig. 140.—Chronic peptic ulcer.

and may be overhanging. The floor is hard and indurated.

Reference may be made here to the appearance of the lesion as seen with the gastroscope. Normal gastric mucosa presents a brilliant picture, glistening and orange-red. A gastric ulcer has a yellow or greyish-white floor, an abrupt edge, and the entire lesion is sharply circumscribed. In a malignant ulcer, on the other hand, the floor is dark brown or violet, the edge ragged and irregular, and the surrounding mucosa appears rigid and grey (Schindler). The colors as seen through the gastroscope are more intense than in the gross specimen due to the circulating blood and the bright illumination.

The morbid anatomy of *duodenal ulcer* is similar to that of gastric ulcer. The ulcer is almost always situated in that portion of the first part of the duodenum known as the duodenal bulb or pyloric cap, which is more or less filled with acid chyme. The ulcer causes a characteristic deformity of the duodenal cap as seen in the roentgenogram (Fig. 141). The

ulcer is situated on the anterior or posterior wall in about equal proportion. The ulcer may be acute or chronic. A diagnosis of acute duodenal ulcer is made very much less frequently than one of acute gastric ulcer; for one thing hemorrhage is a much rarer complication in the former than in the latter. It is probable, however, that many cases which pass under the guise of hyperchlorhydria are in reality acute duodenal ulcers. Acute ulcers are not uncommon in children, and are then usually associated with some septic focus elsewhere. The ulcers associated with burns are of the acute type, and are probably due to sepsis. For this reason they are seen much less frequently now than formerly. These ulcers, first described by Curling in 1842 (Curling's ulcer), generally appear from 6 to 12 days

Fig. 141.—Duodenal ulcer with marked deformity of first part of duodenum.

after a severe burn, as a rule in the first part of the duodenum. They tend rapidly to perforate, to cause hemorrhage, or to heal; they rarely become chronic.

It may be difficult to determine the exact site of the chronic duodenal ulcer in relation to the pylorus, and in the past many of these ulcers have been wrongly regarded as occurring on the gastric side of the pyloric ring. Moynihan has pointed out that in the operating room the position of the pylorus is indicated by the pyloric vein which forms a complete venous ring. There may, of course, be an ulcer on both sides of the pylorus. On the peritoneal surface the ulcer is indicated by a thick white scar, which may be appreciated better by the fingers than by the eye. It is

usually situated on the anterior surface. For this reason adhesions to neighboring organs are less likely to form than in the case of gastric ulcer, so that perforation is more liable to occur. The appearance when viewed from within is the same as that of gastric ulcer, but the duodenal ulcer is usually smaller, and seldom attains to any great size. As the result of cicatricial contraction small diverticula are of frequent occurrence, situated nearly always between the ulcer and the pylorus. When the ulcer is on the anterior or the posterior surface this pouching is generally bilateral; when the ulcer is on the anterolateral surface the pouching is unilateral. Robertson and Hargis point out that one result of the cicatricial contraction is a shortening of the first part of the duodenum. The normal distance from the pylorus to the papilla is 8 cm., but in old or healed ulcers it is reduced to 6.5 cm. or even 6 cm. This shortening may serve as a valuable indication of the presence of a healed

Fig. 142.—Gastric ulcer showing inflammatory foci in base. × 40.

ulcer which would otherwise pass undetected at autopsy, but I have found many exceptions to this rule.

Microscopically the four zones described by Askanazy can readily be made out in well fixed surgical material although in autopsy specimens little or no acute inflammation may be recognized. These zones are the zones of exudation, of necrosis, of granulation, and of cicatrization. In the earlier ulcers collections of polymorphonuclears may be found in the surface exudate and in the necrotic and granulation tissue layers. In the more chronic ulcers the cells are mainly lymphocytes and plasma cells.

The zone of necrosis varies in thickness, advancing at the expense of the underlying zone of granulation tissue. In it there are the usual cytoplasmic and nuclear changes characteristic of necrosis, as well as hyaline masses which may be derived from the necrotic connective tissue. The granulation tissue zone calls for no special comment.

The zone of scar tissue forms one of the most important features of a chronic peptic ulcer. It constitutes the base of the ulcer, and extends laterally in the form of a dense wedge, the base of which rests on the edge of the ulcer. It is evident, therefore, that it extends for some distance under the intact mucous membrane, and it is probably an important factor in preventing the approximation of the edges and therefore interfering with healing.

When one examines a series of chronic ulcers one is struck by the signs of active inflammation which are found in even the least active looking specimens. Both in the scar tissue and in the surrounding mucosa the vessels are dilated, and there are numerous groups of inflammatory cells, either acute or chronic in type. It is evident that the process of irritation is by no means over (Fig. 142).

Vascular lesions are frequent both in the ulcer and in the surrounding tissue. Arteritis and periarteritis are merely part of the inflammatory process. Obliterating endarteritis often associated with thrombosis is common. It is of great importance to bear this in mind, for many ulcers have been declared syphilitic merely on the evidence of an endarteritis and periarteritis which may be found in any chronic peptic ulcer.

The nerves as well as the arteries are injured by the extension of the ulcer. A neuritis and perineuritis may be observed both in the floor of the ulcer and at a distance. The ganglion cells disappear, and the nerve fibers may become coiled up into masses resembling amputation neuromata. These changes in the nerves are of interest in relation to the all important subject of pain, but, although the idea of the acid gastric juice acting upon the inflamed nerves with the production of pain is a seductive one, it appears more probable that the real cause is to be sought in spasmodic contraction of the muscular wall.

At the margin of any chronic peptic ulcer evidence of proliferative activity on the part of the epithelium may be observed. This takes the form of downgrowths into the deeper tissues. Some of these changes, however, and especially the presence of glandular tissue beneath the muscularis mucosae, appear to be due to distortion produced by contraction of the scar tissue. Although carcinoma may undoubtedly develop on top of a peptic ulcer, it is most important that these secondary changes should not be mistaken for a true malignant neoplasia.

Healing.—It is common knowledge that acute ulcers and erosions heal rapidly and with ease. But there can be little doubt that many chronic ulcers also heal completely. Crohn and his associates have shown by roentgenological studies that the crater may disappear completely, although this is not conclusive proof that healing has occurred. If the stomach is searched systematically at autopsy scars may be found as frequently as active ulcers. An ordinary peptic ulcer seldom attains to any great size, and is usually under 2 cm. in diameter. It tends to penetrate deeply rather than to extend widely. Crohn has shown by means of the X-ray that many ulcers attain their maximum diameter in the course of a few weeks.

The difficulties in the way of healing have already been alluded to. The mucinous exudate and the layer of necrotic material provide no footing for ingrowing epithelium. The dense scar tissue interferes with

an approximation of the edges. But the most potent factor is the action of the acid gastric juice. It is the diversion of this material by the operation of gastro-enterostomy which gives an ulcer at the pylorus an opportunity to heal.

The most valuable contribution to our knowledge of the healing process has been made by Mann. His method of producing a chronic peptic ulcer in the jejunum by draining the alkaline duodenal secretion into the lower part of the ileum has already been described (page 223). After the site of the ulcer was explored, and measurements were taken, the pyloric opening was closed, and the stomach drained by a gastrojejunostomy. The ulcer was thus no longer subjected to the action of the unneutralized acid gastric juice.

The subsequent changes may best be given in Mann's own words. "Following this procedure the ulcers healed with remarkable rapidity. Within four days their bases were clean. In ten days the ulcers had usually greatly decreased in diameter and depth, and the mucosa had begun to grow in from the edges. On the twentieth day three-fourths or more of the base of an ulcer was covered with mucosa. Before the thirtieth day it was almost impossible to find the site of a lesion. An ulcer, 1.5 cm. in diameter and 0.5 cm. in depth, which had perforated the entire thickness of the jejunal wall, would almost entirely disappear within twenty-five days after protecting it from the gastric contents. The base, which was hard and indurated, became soft and thin, sometimes bulging like the wall of a diverticulum."

By further experiments it was shown that the greater part of the benefit was due to the protection of the ulcer from the acid gastric juice. The mechanical action of the secretions pouring over the ulcer was also shown, however, to be a factor of some importance in preventing or retarding the healing.

"Macroscopically the first evidence of healing was the disappearance of exudate and débris from the base. The ulcer appeared to grow shallow, due to a filling in of the base by new granulation tissue, which, together with the overhanging edges of mucosa, completely filled the base. Gradually the edge of mucosa grew from the periphery towards the centre, usually pushing the granulation tissue up and out like a plug. At first the mucosa was thin and smooth, but it gradually thickened and was thrown into folds. The inflammation in the base subsided and the hard induration disappeared. Microscopically the development of the granulation tissue and the growth of the mucosa and connective tissue could be closely observed. As the base of the ulcer became clean, the leucocytes disappeared, and granulation tissue developed, which was usually very vascular. The mucosa grew in from the edges over the surface of granulation tissue. At first the mucosa consisted of but a single layer of flat or cuboidal cells. Later the cells became typically columnar. The growing edge of mucosa was very fragile, and it can readily be seen how easily it would be destroyed by the passage of the gastric contents over it."

From this work it is evident that the acid gastric juice is the essential factor in the prevention of healing. This has been for long suspected, but Mann's work has placed the matter on a sure experimental foundation on which the clinician may build. This histological examination

showed that the healing processes were active in the ulcers at all times, but when the ulcer was unprotected from the gastric contents the newly formed cells were destroyed before they could become an integral part of the tissue.

The healing process appears to be essentially the same in man as in the experimental ulcers in the dog. Caylor found that the granulation tissue mushroom was the keystone of the reparative process in human peptic ulcers. If this tuft does not form, the ulcer remains unhealed. A true ulcer does not appear to heal by epithelial outgrowth from the margin alone. It seems likely that many ulcers heal, recur, break down, become more fibrotic, heal again, and so on. With each recurrence the ulcer becomes deeper, and the blood supply more poor, so that the granu-

Fig. 143.—Perforated gastric ulcer—gross.

Fig. 144.—Perforated duodenal ulcer—microscopic. × 8.

lation tissue tuft is formed with greater difficulty, till at last it is not formed at all.

One difference may be noted between gastric and duodenal ulcers as regards healing. Many chronic gastric ulcers heal without a grossly demonstrable scar, whereas duodenal ulcers, which tend to be deeper, leave a scar which is easily recognized and often deforming. It is not only in adults that the process of healing may be observed. Many cases of melena neonatorum are due to the presence of duodenal ulcers which can be demonstrated at autopsy. These ulcers, however, heal rapidly, and if the child lives for a short time, the defect in the mucosa may be completely covered over. I have observed a completely healed gastric ulcer in an infant three weeks old.

Complications.—The four complications of peptic ulcer are: (1) perforation, (2) hemorrhage, (3) cicatricial contraction, and (4) carcinomatous change. The last-named is considered under a separate heading.

Perforation is the natural termination of an ulcer which continues to penetrate the deeper tissues (Figs. 143 and 144). Perforation is generally seen in ulcers with a history of from a few days to a week, in which there is rapid penetration of the deeper coats. Ulcers of long standing with abundant scar formation are much less liable to perforate. Ulcers with continuous symptoms are more dangerous than those with intermissions, for in the former there is no healing and little fibrosis. A chronic ulcer may perforate into the peritoneal cavity, but often the perforation is into one of the neighboring solid viscera to which it becomes attached by inflammatory adhesions. As the ulcer is usually on the posterior wall the organ to which it is most frequently attached is the pancreas or liver. An indurated mass may be formed in the pancreas, but in the liver necrosis and abscess formation are more common. Perforation may occur into the lesser sac, leading to a localized peritonitis. In one case when I studied

Fig. 145.—Eroded artery in gastric ulcer.

the] pus in the lesser sac caused constriction of the transverse colon which was very evident in the X-ray picture.

Hemorrhage is a very frequent complication. It is due to necrosis of the vessel wall, and may occur in an acute or a chronic ulcer (Fig. 145). Depending on the size of the vessel, the hemorrhage may be severe, fatal or a mere oozing. When the hemorrhage is very copious and sudden there may be no vomiting of blood, but at autopsy the stomach is found to be filled with blood clot. Severe hemorrhage may occur in a gastric or a duodenal ulcer. In the stomach the ulcer is usually astride the lesser curvature or involves the pancreas; in the duodenum it is on the posterior wall in the neighbourhood of the gastroduodenal and superior pancreaticoduodenal arteries. No ulcer may be found or aspiration in a case of severe hemorrhage; in these cases, usually young women, there are shallow erosions of the mucous coat due to focal infection. For some unexplained reason, very severe hemorrhage may be followed by disappearance of symptoms and apparent healing for a long time.

Cicatricial contraction is one of the most serious of the late effects At the pylorus it leads to pyloric stenosis with great dilatation of the stomach. On the lesser curvature it produces an updrawing of the greater curvature with partial division of the stomach into two sections, the hourglass stomach. Small diverticula may be formed by contraction of the fibrous tissue.

Malignant Change In Gastric Ulcer.—There are few subjects in the whole range of medicine regarding which more widely diverse views have been held than the relation of gastric ulcer to carcinoma. An ulcer of the stomach may remain benign, it may become malignant, or it may be malignant from the beginning. Some years ago it was believed that very many simple ulcers became malignant, and that very many cancers

started as ulcers. The evidence on which this conclusion was based was primarily pathological. Changes were observed in the edge of the ulcer which were interpreted as indicating a true malignant transformation of the epithelial glands in that area.

The weight of present-day opinion, however, is entirely against this view. The observations of Ewing, Dible, Spilsbury and others make it clear that a very different interpretation may be placed on the microscopic appearance. To one pathologist the presence of isolated epithelial cells and atypical tubules in the neighborhood of an ulcer spells carcinoma, whilst to another they are the result of distortion produced by the contracting fibrous tissue or merely part of the regenerative process. As Spilsbury puts it: "There are commonly found at the edge of the ulcer gland cells which have penetrated deeply into the scar tissue and are

Fig. 146.—Primary carcinomatous ulcer. Malignant gland formation both in edge and base. × 25.

cut off from the regenerating glands. They may exhibit an atypica* glandular arrangement, or may form narrow columns of cells; isolated cells are also seen. It is these cells detached from the regenerating epithelium and buried in the fibrous tissue of the ulcer which are sometimes referred to as precancerous, and which, from their position and irregular arrangement, are regarded by others as indicating malignant transformation of the ulcer."

Ewing found that only 5 per cent of ulcers showed cancer. In 126 ulcers with no clinical suspicion of malignancy Dible found no microscopic evidence of cancer. In cases in which a clinical suspicion of malignancy was entertained, 4 per cent of the ulcers showed carcinoma. In a series of 33 cancers of the stomach in only 5 could the appearance on histological grounds be taken as consistent with development from an ulcer, and even in these it was not at all certain. Dible points out that unless there is

perforation of the muscular coat the carcinoma cannot possibly have arisen from an ulcer. In taking the sections the base of the ulcer must be examined as well as the edge. In an ulcer which has become carcinomatous from the beginning the base as well as the edges are malignant (Fig. 146), whereas in an ulcer which has become malignant the change is found in the edge but not in the base, for the latter is densely fibrous and resists invasion. Tracy Mallory has pointed out a possible fallacy in this reasoning. If a carcinoma in situ, *i. e.*, one confined to the mucosa, undergoes peptic digestion, an ulcer may be produced in which no carcinoma can be found in the base, yet the edges show evidence of carcinoma. Such a finding would wrongly suggest that the lesion had started as a benign ulcer which later became malignant. The malignant change may easily be overlooked in the earlier stages of the lesion. I have seen an ulcer in

Fig. 147.—Prepyloric gastric ulcer, at first benign, now malignant. × 15.

the prepyloric area (always a dangerous region) which appeared microscopically to be perfectly benign, but in the neighborhood of which there was an enlarged lymph node. Sections of this node revealed adenocarcinoma. Only when further sections of the ulcer were made could a commencing cancer be found in the edge at one point (Fig. 147).

The site of election of the lesion suggests that malignant change is not of common occurrence. The majority of cancers are situated at the pylorus, whereas the majority of ulcers are from 2 to 4 inches from the pylorus.

Newcomb gives the following respects in which a simple ulcer differs from a primary malignant one: (1) complete destruction of an area of muscle corresponding to the floor of the ulcer; (2) the presence of a large area of dense fibrous and granulation tissue in the floor; (3) the presence of endarteritis obliterans in the surrounding vessels; (4) fusion of the mus-

cularis mucosae with the muscular coat at the margin of the ulcer. Of these by far the most valuable is the last, and it is the only certain evidence that a cancer has arisen from a previous simple ulcer. Using this criterion Newcomb found that only 13 per cent of cancers showed evidence of an antecedent peptic ulcer, and that 3 to 7 per cent of ulcers showed a malignant change.

It is evident that the solution of this very important problem has foundered on the rock of pathological interpretation. The microscopic picture which to one man means early malignancy means nothing of the sort to another. It is well, therefore, to turn to the clinical evidence. There are two lines of inquiry which may be pursued. First, if cancer so often develops from ulcer both should present a similar history, or rather cancer should be preceded by the history of ulcer. And second, if the danger of ulcer developing into cancer is so great, the subsequent history of many ulcer cases should be one of malignancy.

If the history of a series of ulcer cases be compared with the history of a series of cancer cases a remarkable difference at once becomes apparent. The ulcer cases have as a rule a long history of gastric trouble, whilst the cancer cases have a remarkably short one. The patient with cancer usually gives no previous history of gastric trouble, often he has had a perfect digestion; he may say that until lately he was "able to digest nails." Hugh Maclean analysed the cases admitted to St. Thomas's Hospital over a period of 5 years, and found that whereas the average previous history of symptoms in ulcer was 7 years, in cancer it was only 6½ months. If cancer usually followed ulcer it is obvious that the average cancer history should be at least over 7 years. Dible found exactly the same thing in his investigation. He points out, moreover, that whilst 73 per cent of his chronic ulcers occurred on the lesser curvature, the cancers were closer to the pylorus.

With regard to the second point, Balfour has investigated the after history of 1280 patients who were operated on at Rochester for gastric ulcer. The operation was usually a gastro-enterostomy, so that the ulcer was left in situ. Of these cases less than 6 per cent finally died of cancer. Moreover Balfour is careful to remark that a number of the supposed ulcers may really have been cancer, for the stomach was not opened for exposure of the ulcer at the time of operation. The figure should therefore really be lower than 6 per cent.

This very strong clinical evidence, in conjunction with a formidable weight of pathological material, seems to show that the conception of the frequent transformation of a peptic ulcer into carcinoma should finally be given up. There is of course no reason to doubt that the change does occur, just as it may occur in a chronic ulcer in any part of the body, but it seems probable that not more than 5 per cent of cancers develop from ulcer, and the proportion of ulcers which become malignant is probably very much lower. What is true of the stomach is much more true of the duodenum. Indeed Sir John Bland Sutton remarks "that he has long sought among the living, the dead, and in museums for a duodenal ulcer that has become cancerous; but so far his search has been unavailing."

Clinical Features.—The symptomatology of peptic ulcer is in one sense very simple, and at first sight is easy of explanation. The famous sequence

—food, comfort, pain—can be accounted for by supposing that the pain is caused by a normal or an excess of acid secretion acting upon a sensitive ulcer; the taking of food neutralizes the acid, and when finally this action passes off the pain returns, often in the middle of the night when the stomach is empty, but when the acidity is high. The remarkable relief given by the administration of alkalis tends to support this belief.

But the matter is not quite so simple as this. The taking of food may bring on a paroxysmal attack of pain instead of relieving it. An acute ulcer is frequently unaccompanied by any pain, although the acid juice must act upon the raw surface of the ulcer. There may be long periods of complete cessation from pain, although the X-rays show that the ulcer is still present and is being constantly exposed to the action of the acid. The experimental administration of hydrochloric acid to ulcer patients has given results which vary with the observer. Hurst found that no pain followed the administration of 0.5 per cent HCl, whereas Palmer was able to produce typical ulcer distress by the administration of the same strength of acid in 95 per cent of cases.

Gastric sensations originate in the muscle fibers and are conducted by the nerves distributed to these fibers. It is possible that the painful sensations of peptic ulcer are muscular in origin. The inflammatory foci in the muscularis which have already been described give rise to contractions in the neighborhood of the ulcer and especially at the pylorus. The pyloric hypertonus increases the intragastric pressure and the tension of the muscle fibers, and this increase may be the chief cause of the pain. The relief of pain which follows the use of alkalis may be due to relaxation of the tonus rather than to neutralization of the acid.

In conclusion, there is much to be said both for the acid theory and the hypertonus theory. It is possible that both factors may play a part in different cases.

Laboratory examinations may be of value in the diagnosis of peptic ulcer, but of these the examination of the stool for occult blood is much more useful than the universally employed gastric analysis. If a weak half per cent solution of benzidene is used, there will be no reaction for blood to any of the foods except large rare beef steak, which is not likely to be on the menu of the peptic ulcer patient. The center of the fecal mass is tested to avoid blood from bleeding hemorrhoids and anal fissures. It must be remembered that cancer of the stomach as well as other gastro-intestinal lesions may give blood in the stool. As regards gastric analysis, the most important information obtained by the stomach tube is the examination of the fasting contents 6 or 7 hours after a meal, a method which reveals delayed emptying time at a lower cost than by X-ray examination. The average curve of acidity of fasting contents in normal persons ranges from 15 to zero, in gastric ulcer from 20 to 60, and in duodenal ulcer from 40 to 60. The usual procedure of examining a single sample about an hour after eating crackers or toast and water is of little value, as the acid range of normal individuals overlaps to a large extent the acid range of peptic ulcer patients.

Secondary Jejunal Ulcer.—This is a complication of gastro-enterostomy performed usually for duodenal ulcer, sometimes for gastric ulcer. It is almost unknown after gastro-enterostomy for cancer of the stomach.

These facts indicate the importance of high gastric acidity in the causation of the condition. It is most likely to recur when the stomach shows hypermotility (rapid emptying) and hyperacidity. The frequency is usually given as from 2 to 3 per cent of cases of gastro-enterostomy. It is very much commoner in men. Two forms are recognized, the jejunal and the gastrojejunal. Both may be included under the term anastomotic ulcer. The jejunal ulcer generally occurs in the efferent loop of bowel, usually within one inch of the stoma. It may occur at the stoma. It is rare in the afferent loop owing to the presence of alkaline juice from the duodenum. The gastrojejunal ulcer is situated in the line of the anastomosis or abuts on it. The two forms are equally common. The ulcer seldom develops in less than 6 months. The great majority give rise to symptoms in from 6 months to 2 years after the operation. Occasionally the interval is much longer, even 10 or 15 years.

The characters of the ulcer are the same as those of an ordinary peptic ulcer. The ulcer may heal, erode a vessel, or perforate. Spontaneous healing is rare, and the resulting fibrosis may lead to a severe degree of stenosis. Wright points out that if the gastro-enterostomy has been of the anterior type the ulcer tends to adhere to the anterior abdominal wall, and a large tumor is produced in this situation. In the ulcer following the posterior type of operation the inflammatory mass is not so evident, because it is hidden behind the colon and mesocolon. *Perforation* into the abdominal cavity is not common, but perforation into the transverse colon occurs in about 10 per cent of the cases, with the establishment of a jejunocolic fistula. This is characterized by the occurrence of intense uncontrollable diarrhea and the appearance of a large amount of undigested food in the stools. The presence of a fistula is indicated by the passage of a barium enema into the stomach. When a fistula is established the ulcer generally heals. If the gastro-enterostomy is undone the jejunal ulcer quickly heals, but there is a danger that another gastric or duodenal ulcer may form.

The *etiology* of the condition is uncertain. There is no doubt that the action of the highly acid gastric juice on the mucosa of the jejunum is the essential factor, but, as in the case of peptic ulcer, there must be some accessory factor. It seems probable that this is of the same nature as the factor responsible for the necrosis which led to the original peptic ulcer, probably a focal infection. In the past it has been customary to blame the presence of unabsorbable suture material such as silk or linen, but it is now certain that this factor has been greatly overemphasized.

Chronic Follicular Gastritis.—It sometimes happens that a patient shows all the symptoms of the ulcer syndrome, including hemorrhage, but when the stomach is opened no ulcer can be found. In such cases it is not infrequent to find a chronic follicular gastritis, a lesion which may give all the symptoms of ulcer, and which is most readily studied when a partial gastrectomy has been done. The condition is well defined by Fitzgerald as "an inflammatory change in the stomach wall of long duration, with variable gross characteristics but constant microscopic appearances, and a clinical course marked by dyspepsia and often by hemorrhage." Many cases of gastrostaxis, or bleeding from the stomach with no discoverable lesion, are examples of this condition. Loss of blood is a marked feature, but the amounts are small (occult blood in stomach contents and stools).

The lesions are most marked in an area usually confined to the pylorus and pyloric antrum, and are patchy in distribution. The most constant gross finding is a thickening and stiffening of the wall in the pyloric region. The overlying serosa generally shows a

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reddish blush. When the stomach is opened a thick layer of slimy mucus is seen to be adhering to the affected mucosa. There may be minute hemorrhagic erosions, or irregular worm-eaten patches of partial destruction of the mucosa.

Microscopically there is a marked infiltration of the mucosa by inflammatory cells; the arrangement is both diffuse and focal. The cells of the exudate are eosinophils, plasma cells and lymphocytes. The latter are collected into follicles with well marked germ centers These follicles form the outstanding feature of the microscopic picture. The surface epithelial cells are filled with mucin. Later there may be atrophy and cyst formation. *A constant change is thickening of the muscularis mucosae.* The hemorrhagic erosions are clefts which cut through the mucosa and may reach the muscularis mucosae. The thickened mucous membrane may develop polypoid processes, a condition known as *gastritis polyposa.* The etiology of follicular gastritis is unknown.

In the diagnosis of gastritis X-ray relief technic is disappointing and gastric analysis useless The gastroscope, on the other hand, is of great value. In place of the smooth, silk-like, orange-red normal mucosa, there are layers of white, grey or green mucus on the surface or hyperemic spots, the same appearance observed by Beaumont in the open stomach of Alexis St. Martin one hundred years ago.

There is marked difference of opinion as to the relation of chronic gastritis to ulcer. Some observers, notably Hurst, believe that gastritis is a common precursor of ulcer; others deny any relationship.

Duodenitis.

In 1921 Judd pointed out that in some cases which presented a typical clinical picture of duodenal ulcer no crater could be found, but a condition of congestion and stippling of the serosal surface, sometimes with pin-point mucosal ulcers. This condition is known as duodenitis. The simplest form consists of slight hyperemia and faint stippling when the serosa is rubbed at operation. In more advanced cases the area is red, hyperemic and edematous, and serosal stippling is marked. In a still later stage the duodenum is narrowed for several centimeters, although without the stellate scars of a former ulcer. In a case of

Fig. 148.—Acute duodenitis with ulceration.

my own the serosa was normal, but scattered over the first and second parts of the duodenum there was an infinite number of minute superficial erosions of the mucosa (Fig. 148). *Microscopically* the epithelium is generally intact, but it may be denuded in a few small areas. In the mucosa and submucosa there is an infiltration of lymphocytes, plasma cells and occasional eosinophils. Sometimes the infiltration extends through the muscular layers to the serosa. The latter coat is thickened and markedly congested. There is no constant etiological factor. The duration may be measured in weeks, months or years. The importance of the condition lies in the fact that it may mimic duodenal ulcer, although there are radiological distinctions. In my own case and in a number of others that have been reported an unexplained symptom was marked dyspnea.

CARCINOMA

Carcinoma of the stomach is the commonest form of malignant tumor affecting the internal organs. In Great Britain it is nearly three times as common as cancer of the uterus and twice as common as cancer of the breast. Moreover, on account of its remarkable silence the cure-rate is the worst in malignant disease. Ogilvie gives the following somber picture. Of patients presenting themselves to hospital about 50 per cent are clearly beyond treatment of any kind on account of widespread metastases. Of those submitted to laparotomy about 40 per cent are beyond any surgical treatment, 20 per cent admit of a palliative operation only, and 40 per cent are suitable for radical resection. The average age period is about 60. Many cases, however, occur between 30 and 40, and it may be met with as early as 20.

The common *site* is the prepyloric region, where 70 per cent of cancers occur. (The prepyloric region is the last inch of the stomach, but does not include the pylorus.) As benign ulcers are comparatively infrequent in

Fig. 149.—Polypoid form of carcinoma of stomach.

the prepyloric region it follows that an ulcer in this area should be regarded as malignant until proved to be innocent. About 25 per cent of the remaining tumors occur on the lesser curvature, and 5 per cent in the fundus.

The only *etiological factor* of any importance with which we are acquainted is peptic ulcer. The question as to the relative frequency with which carcinoma develops on top of a simple ulcer has already been discussed on page 232. The relationship of trauma to carcinoma of the stomach is sometimes brought up in Workmen's Compensation cases. In spite of instances cited to the contrary it cannot be said that there is any reasonable support for this idea.

There is no very satisfactory method of classifying the various forms of cancer of the stomach. Kaufmann and other pathologists adopt a histological basis. As regards the malignant cell, two chief types may be recognized, the cylindrical cell tumors and the spheroidal cell tumors. The former may occur as an adenocarcinoma, or the cells may be arranged in solid masses. The spheroidal cell growths are more likely to give

rise to a diffuse infiltration. In both of these the amount of connective tissue stroma is very varying. When it is abundant and the cells are scanty the tumor is of the scirrhous type. Either the cylindrical cell or the spheroidal cell tumors may be the seat of gelatinous degeneration, with the formation of the so-called colloid cancer.

From the standpoint of the clinician more is to be gained by employing a gross rather than a microscopic classification. Three main types may be recognized. These are (1) papillary, (2) ulcerating, (3) diffuse infiltrating.

The Papillary Form.—The tumor forms a large, soft, polypoid mass (Fig. 149) which may arise in any part of the stomach, but is found most
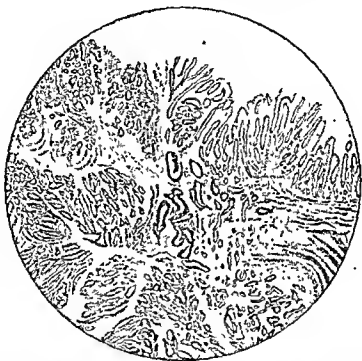
Fig. 150.—Adenocarcinoma of stomach. There is a very sudden change from the normal mucosa to the wildly proliferating epithelium. The cells of many of the new glands stain darkly.

frequently near the pylorus. Projecting like a mushroom into the cavity of the stomach it may give rise to remarkably little disturbance unless it happens to produce obstruction from its situation. When the surface becomes ulcerated and infected, the classical but late symptoms of carcinoma of the stomach make their appearance, such, for instance, as cachexia, severe anemia, and hemorrhage.

Microscopically the tumor is an adenocarcinoma (Fig. 150). It is composed of fairly well formed glandular tubules which replace the normal mucosa, penetrate through the muscularis mucosae, permeate the submucosa, and may finally appear in the subserous layer (Fig. 151). The tubules are often only lined by a single layer of epithelial cells, so that

some sections may suggest the appearance of an innocent adenoma. The malignant cells, however, are usually different from the normal cells, their nuclei are larger and darker (more hyperchromatic), so that the
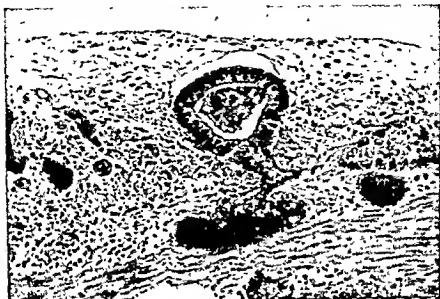
Fig. 151.—Carcinoma of stomach showing invasion of serous coat which is almost perforated. × 125.

Fig. 152.—Adenocarcinoma of stomach showing glandular formation in muscularis, much of which is still intact. × 75.

acini appear much darker than the normal tubules and can as a rule be readily distinguished from them. It should be noted that in this and other forms of carcinoma the muscular coat, although destroyed, is seldom

completely replaced, so that portions of it can be recognized in the section (Fig. 152). In this respect cancer differs from peptic ulcer, for in a penetrating ulcer all trace of muscular tissue disappears.

Fig. 153.—Carcinomatous ulcer of stomach.

Fig. 154.—Ulcer of stomach with carcinomatous change.

This form, although presenting a markedly malignant appearance to the naked eye, is relatively benign compared with the more infiltrating types, and the prospects of the patient after surgical removal are considerably better. Lymph node involvement occurs later, and insidious dissemination throughout the stomach wall is less pronounced. Some of

the cases no doubt arise as a malignant transformation of an adenomatous polyp, which may act as a precancerous condition.

The Ulcerating Form.—This is the usual form of cancer of the stomach. It occurs principally at the pylorus and also on the lesser curvature. Instead of forming a large bulky mass, the tumor is only slightly elevated and early becomes ulcerated. The edges of the ulcer are raised and rounded, and it may assume much larger proportions than the peptic ulcer (Fig. 153). MacCarty's dictum that *if an ulcer has a diameter greater than 2 cm. it is likely to be malignant is a fairly safe one to follow* but there are many exceptions.

The peptic ulcer which becomes malignant belongs to this variety (Fig. 154). The differentiation may have to be made by the microscope. Both the edge and the base must be examined. In the simple ulcer which

Fig. 155.—Carcinoma of stomach. Three dilated lymphatics in submucous coat filled with malignant cells. × 75.

has become malignant, the malignant change is found in the edge; the tumor cells are unable to invade the dense fibrous base. In the carcinoma which has become ulcerated malignant cells are found in the base as well as in the edge.

The cut surface shows marked thickening of the stomach wall, on which yellow flecks of necrotic material may be seen. There may be tumor nodules on the serous surface, and involvement of the regional lymph nodes and the omentum.

There is no constant microscopic picture, but usually the malignant cells are arranged in solid masses or columns. The mucosa is replaced by these masses and the submucosa extensively infiltrated (Fig. 155). It is seldom, however, that the muscularis is completely destroyed as it is in peptic ulcer. In carcinoma developing on top of a peptic ulcer there will of course be complete destruction of the muscularis. The fibrous

stroma may be very abundant, so that such growths come into the class of scirrhous. In other cases the picture may be one of adenocarcinoma or spheroidal cell carcinoma.

The Infiltrating Form.—In this variety, there is no real tumor to be seen. Instead there is an infiltration and induration of the stomach wall which may be local or diffuse (Fig. 156). The local form is seen at the pylorus, where a dense ring of sclerotic tissue is formed around the opening, and by its contraction gives rise to an intense degree of stenosis with accompanying dilatation of the stomach. On section the wall is greatly thickened and densely hard. *Microscopically* the picture resembles that of a scirrhous cancer of the breast. The epithelial cells are scanty,

Fig. 156.—Leather-bottle stomach, showing small size of stomach with extreme thickening of wall.

and the small groups or columns are separated by an extremely abundant stroma.

The diffuse variety is of particular interest. In 1854 Brinton applied the name linitis plastica to a condition in which the stomach showed a peculiar thickening of the entire wall with great contraction of the lumen. The cut surface displayed glistening filaments like woven linen, and it was on account of this appearance that Brinton used the name linitis. He considered it "an inflammation of the filamentous network of areolar tissue ensheathing the vessels." Many names have been applied to this condition, such as leather-bottle stomach, cirrhosis of the stomach, and fibromatosis of the stomach. By some it has been regarded as syphilitic, by others a form of hyperplastic tuberculosis similar to that which occurs

in the cecum. The evidence is not sufficient to enable one to be dogmatic, but it appears probable that there are two main types, the one a carcinomatosis and the other a fibromatosis. In the latter there is an extreme fibrous thickening of the submucosa with involvement of the muscle. Collections of leucocytes and eosinophils are scattered throughout the fibrous tissue. The mucosa may be well preserved or may be extensively destroyed. Whether this fibromatosis is neoplastic or inflammatory it is not possible to say. Most cases of leather-bottle stomach are examples of diffuse carcinomatosis. The malignant cells are scattered diffusely throughout the wall of the stomach where they excite an extreme degree of fibrosis. The carcinomatous cells are usually small in numbers, so that many sections may have to be examined before definite evidence of malignancy can be found. Single rows of cells may be mistaken for plasma cells.
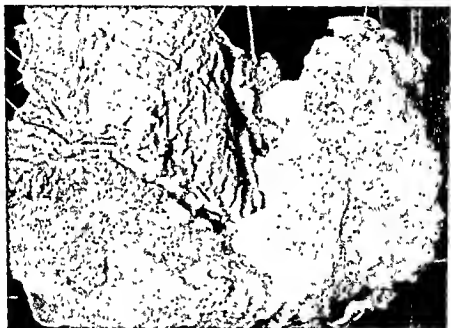
Fig. 157.—Mucoid carcinoma of stomach.

The gross appearance of the leather-bottle stomach is very characteristic. Although it is considered probable that the process commences at the pylorus and extends from there, by the time the patient comes under observation the entire stomach is usually involved. The stomach is very small and very thick walled. The normal stomach is about 12 inches long and contains about 40 ounces; the leather-bottle stomach may only measure 4 inches and contain 4 ounces. The wall may be as much as an inch thick. The whole stomach is often involved from the cardia to the pylorus, but the thickening stops abruptly at the pyloric ring and does not invade the duodenum. The thickened pylorus may project into the duodenum like the cervix uteri. There is, however, no pyloric obstruction. Indeed the stomach behaves merely as a rubber tube, and the barium meal can be seen to pass straight through it and drop into the duodenum, thus enabling a diagnosis of the condition to be made.

involved, but the nodes on both sides or on the right side alone may be affected.

(3) The *neighboring organs* usually involved by direct spread are the liver and pancreas. The liver is invaded in about a third of the cases, either by direct spread or by the portal vein. The omentum may be extensively invaded with the formation of a large mass.

(4) Spread *through the peritoneal cavity* is due to tumor cells perforating the serous coat of the stomach and being set free. They become seeded over the peritoneum and pelvic organs, taking root with particular ease upon the ovaries which are involved in from 2 to 3 per cent of cases. The ovaries are peculiarly liable to infection, having an open wound on the surface at each menstrual period. The ovarian tumor may be taken for a primary growth. It shows the characteristics of the Krukenberg tumor, with marked gelatinous degeneration of the cells and displacement of the nucleus to one side so as to give a signet-ring appearance.

(5) *Blood* spread is most often to the liver. The lungs, bones and brain may also be involved, less frequently the other viscera.

The Relation of Symptoms to Lesions.—*Pain* as an early symptom is absent in about 50 per cent of cases. The infiltration of the muscularis by the tumor cells is a slow and insidious process which does not irritate the neuromuscular mechanism to a degree sufficient to produce the sensation of pain. Pain is most likely to be severe in ulcero-carcinoma, the condition which is at first a peptic ulcer and then becomes malignant. In this form spasm is a marked feature and is responsible for the pain.

Loss of appetite is an early symptom. The slow infiltration of the muscular wall by tumor cells interferes with the healthy tone on which the sense of appetite depends. A feeling of fullness after meals is due to the same cause.

Absence of free HCl is probably due to the secondary changes which develop in the rest of the mucosa, leading to atrophy of the acid-producing (oxyntic) cells. In early carcinoma free HCl is often present, and it can be demonstrated in 50 per cent of cases if the fractional method is used. This is in great contrast to pernicious anemia.

Blood either in the stomach contents or in the stool (occult blood) is most often found in ulcero-carcinoma, but is quite common in primary carcinoma with ulceration. The severe hemorrhage of gastric ulcer is seldom seen, because the lesion is not a perforating one.

Anemia may be present even in the early stages. It is usually secondary, but sometimes primary in type. The secondary anemia is caused by septic infection of the surface, and by loss of blood from the ulceration. The primary form with a blood picture of pernicious anemia may be due to a nutritional defect which interferes with the formation of red blood cells just as in pernicious anemia. In view of the severity of the local lesion it is remarkable that this form of anemia is not more common.

The *X-rays* have opened up great possibilities in the early diagnosis of gastric carcinoma. In skilled hands (an important consideration) a correct diagnosis may be made in as much as 90 per cent of the early cases, and in every case at a more advanced stage. In the proliferative or bulky type the tumor projecting into the lumen is seen as an irregular filling defect (Fig. 159). When there is obstruction at the pylorus there

will be delayed emptying of the stomach. In the infiltrative type, usually involving the pylorus, there is interference with pyloric closure. Wherever the wall of the stomach happens to be infiltrated there will be cessation of the peristaltic wave seen on the screen. The degree of stomach involvement and the question of operability may also be decided with a fair degree of accuracy.

Curability.—It is difficult from a study of statistics to say what exactly are the prospects of cure which the surgeon can offer a patient. In a series of selected cases the results may be fairly encouraging. Ogilvie remarks that we may find cause for satisfaction in the general advance of surgery during the last decade, but upon the subject of cancer of the stomach we can only look with gloom, that the operability in cases of patients presenting themselves with symptoms is lower than with any other growth,
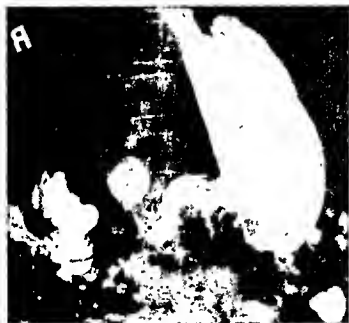
Fig. 159.—Carcinoma of the stomach, showing great deformity of the greater curvature towards the pylorus.

and that we should write up in neon lights in every restaurant, "Indigestion does not start after 40 in a man who has been able to eat anything till then."

Carcinoma of the Duodenum.—Cancer of the duodenum is remarkably rare in comparison with the similar disease of the stomach. Deaver has collected figures of 151,201 autopsies, and in only 50 of these was duodenal carcinoma found.

The usual site for the tumor is the second portion of the duodenum, due probably to the presence of the ampulla of Vater in that part. The ampulla or its immediate neighborhood is a common starting point of the disease. The relative frequency of the various sites is given by Deaver as follows: first part, 22.15 per cent; second part, 65.82 per cent; third part 12.03 per cent.

Carcinoma of the first portion usually arises as a malignant degeneration of a chronic duodenal ulcer. Such an occurrence, however, is very rare compared with the case of ulcer of the stomach. The characters of the growth are similar to those of gastric carcinoma. Usually the tumor is of the flat ulcerating variety. Cancer of the second portion is frequently associated with dilatation of the biliary and pancreatic ducts, with the production of jaundice and the formation of pancreatic retention cysts. In one example of the disease which has come under my notice the dilatation both of the bile and the pancreatic ducts was so pronounced as to be one of the chief features at the autopsy. When the liver was cut the bile ducts could be seen standing out in a remarkable manner, the surface of the pancreas was covered by numerous cysts about the size of a pea, and the main pancreatic duct was greatly dilated.

SARCOMA

Sarcoma of the stomach is a rare condition, which may take several forms. The myosarcoma forms a well-defined group resembling the myosarcoma of the uterus. The tumor is usually large, projects into the cavity of the stomach, and soon becomes ulcerated. In another group the tumor is not a true sarcoma, but a local manifestation of lymphosarcoma or Hodgkin's disease, which may begin in the lymphoid tissue of the stomach or in some other part of the lymphatic apparatus. Other sarcomas are of a more indeterminate nature, and may be classed as round celled or spindle celled.

INNOCENT TUMORS

A number of different benign tumors occur in the stomach. All of them are rare. The figures from the Mayo Clinic show that less than 0.5 per cent of gastric tumors are benign. The commonest is a myoma, similar in structure to the leiomyoma of the uterus. The tumor s nearly always single, and, arising from the muscular layer, may project into the lumen or into the peritoneal cavity. It may attain a great size, sometimes as large as a man's head. When situated near the pylorus it may pass through into the duodenum. Occasionally it may undergo a malignant change, becoming a myosarcoma. Other innocent tumors which merely need to be mentioned are fibromas, fibro-adenomas, lipomas, and hemangiomas.

A condition of rather special interest is that known as *diffuse gastric polyposis*. The term polyposis must not be taken to indicate a pathological entity, for polypoid masses may be either neoplastic or inflammatory in nature. In most cases, however, the nodules are adenomatous. These form soft discrete polyps which may be scattered over the entire mucosal surface, but are often localised to one area, usually the greater curvature and the lower third of the stomach (Fig 160). In one case which I studied, the tumors, ranging from the size of a cherry to that of a pea, formed a ring around the stomach from one to two inches from the pylorus.

Fig. 160.—Polyposis of stomach.

The duodenum is never involved. Microscopically there is an orderly arrangement of new-formed glands, many of which may show cystic dilatation (Fig. 161). The X-ray picture is characteristic, showing irregular defects in the margin of the gastric shadow along the greater curvature, the indentations having ragged edges (Fig. 162). Two of the most constant clinical features are severe anemia and achylia gastrica. A small

number of the cases become malignant. In addition to these multiple adenomata there may be a hypertrophic condition of the gastric mucosa, which is thrown into great
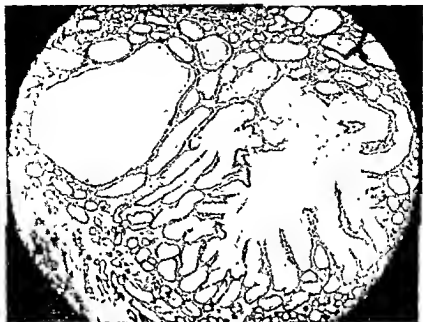
Fig. 161.—Gastric polyposis showing glandular formation. × 50.

Fig. 162.—Polyposis of the stomach.

folds resembling the convolutions of the brain. This must be regarded as inflammatory in nature, and is probably related to hypertrophic gastritis. In one case I found that the swelling was largely due to edema.

TUBERCULOSIS OF THE STOMACH

Tuberculosis of the stomach is a rare disease. Tubercle bacilli swallowed in the sputum or in tuberculous milk tend to be killed by the gastric juice if they remain in the stomach. There may be hematogenous infection of the stomach wall from some primary focus elsewhere. The lesions may take the form of an ulcer or a tumor, usually the former. The ulcer has ragged and undermined edges. It seldom extends beyond the submucous coat, so that perforation is rare. When the lesion takes the form of a tumor there may be no ulceration, merely caseation below an intact mucosa. Unless there are tubercles on the serous surface it is seldom possible to make a correct diagnosis from the gross appearance, and the lesion is often mistaken for peptic ulcer or cancer.

SYPHILIS OF THE STOMACH

Syphilis of the stomach used to be regarded as a very rare condition, yet a large number of cases have been reported in the recent literature. The explanation is to be found in the strictness of the standards by which the diagnosis is judged. Chiari in 1891 insisted that we must have definite histological evidence before a diagnosis of gastric syphilis can be accepted, but this view has been lost sight of in these days of the Wassermann reaction and X-ray diagnosis. As Hartwell remarks, there is a world of difference between a syphilitic ulcer and ulcer in a syphilitic. The Wassermann reaction and the X rays are powerless of themselves to make this distinction.

When judged by the rigid standard of histological diagnosis the number of genuine cases becomes very much smaller. As a matter of fact it is by no means easy to say even under the microscope if a piece of the stomach wall is or is not syphilitic. Turnbull of the London Hospital points out that any of the changes commonly found in syphilitic lesions may also be present in an ordinary peptic ulcer; there may be the same infiltration with plasma cells, lymphocytes, and eosinophils, the same endarteritis, and even giant cells may be found. The only incontrovertible proof that an ulcer is syphilitic is the demonstration in its wall of the Spirochaeta pallida, and this has been done only on one occasion, namely in the case reported by McNee. Even in this case McNee only found the spirochetes in one block of tissue out of eight.

In spite, therefore, of some recent contributions we must continue to look upon syphilis of the stomach as a very rare condition. In 4880 autopsies at Bellevue Hospital there were 316 examples of advanced syphilis but only one case of syphilis of the stomach. In 13,000 autopsies at the London Hospital Turnbull was unable to find a single undoubted case.

The disease appears to commence as a gumma in the submucosa, and this in time breaks down and forms an ulcer. In McNee's case the ulcer was very large, extending from the cardia to the pylorus along the lesser curvature and involving much of the greater curvature. Indeed only two-fifths of the stomach was free from ulceration. The chief characteristic of the ulcer were its very irregular outline and its greatly thickened edges. The stomach wall was from ½ to ¾ inch thick, and on section showed the dense pearly white appearance of scirrhous carcinoma. There was marked endarteritis obliterans in the vessels.

The cases may be arranged in three clinical groups: (1) those which give a history suggestive of gastric ulcer, (2) those which resemble carcinoma, and (3) atypical cases. The most likely diagnosis to be made is carcinoma. The gastric acidity is said to be low, and blood is apt to be present when ulceration has occurred.

HYPERTROPHIC PYLORIC STENOSIS

The child with congenital pyloric stenosis, usually a male breast-fed infant and often the first-born in the family, does quite well for a week or two, then commences to vomit. The vomiting may subside in the course of a few weeks, or it may increase in frequency and severity and continue for months, unless death cuts short the course of the disease. Even a few drops of food may precipitate the vomiting. Peristaltic waves can be seen with great distinctness following feeding, or there may be a spastic contraction of the entire stomach accompanied by intense pain. The hardened pylorus can usually be felt as a round, firm, movable mass.

The pylorus is found to be greatly thickened, the thickening extending for a distance of a few centimeters along the pyloric canal. The thickened pylorus projects into the duodenum, but there is no sharp line of demarcation between the thickened portion and the rest of the stomach. The pyloric opening is extremely narrowed, sometimes barely admitting a probe. The opening is filled with closely packed folds of mucous membrane. There is naturally a considerable amount of dilatation of the stomach.

The pyloric thickening is caused by an enormous hypertrophy of the circular layer of muscle fibers. These fibers appear to be increased both in number and size. Sauer has constructed wax models of the musculature of the pylorus, and found that whereas the model of the normal pylorus of an infant weighed 3000 grams, that of congenital pyloric stenosis weighed as much as 6050 grams.

Regarding the exact nature of the condition there is a good deal of difference of opinion. The two principal views are first, that spasm causing narrowing of the pyloric opening and followed later by hypertrophy is the essential cause, and second, that there is a congenital hypertrophy of the pylorus to which spasm is superadded. There are many objections to the spasm hypothesis which has for long held the field, the most fundamental being that the thickening of the pylorus may be found at autopsy months after spontaneous recovery has occurred, or, as in Walton's case, after the pylorus has been put out of action by the performance of a gastro-enterostomy. After the Rammstedt operation, on the other hand, there is marked atrophy of the hypertrophied muscle. The view that the condition is one of congenital hypertrophy must be accepted as the correct one. It has been found in a seven months fetus. The fact that the symptoms usually do not develop for two or three weeks may be explained by assuming that an element of spasm is superadded to the hypertrophy.

ACUTE DILATATION OF THE STOMACH

A surgical complication, as mysterious as it is alarming, is acute dilatation of the stomach. It may occur as a sequel to a surgical operation, or as a complication of some other disease. The operation which it complicates is usually an abdominal one, but occasionally it may be on other parts of the body. The onset may be of dramatic suddenness; in some of the recorded cases the stomach has attained an extreme size in less than a minute. The most prominent symptoms are vomiting, epigastric pain, distension of the abdomen, and collapse.

The stomach, when examined post-mortem, is found to be enormously distended, often extending as far as the symphysis pubis. The contents of the stomach in the early stages are entirely gaseous, but later great quantities of fluid may be present. The two most successful methods of treatment, the use of the stomach tube and the prone position, are designed to combat respectively the accumulation of gas and of fluid. The gastric wall is extremely thin, and the mucosa may be fissured and eroded. The dilatation in some cases ends at the pylorus, in others it extends as far as the point at which the duodenum is crossed by the superior mesen-

teric vessels, whilst in still others it extends beyond that point. The small intestine is collapsed and hangs down into the pelvis.

Etiology.—It used to be thought that the most important factor was the pressure of the superior mesenteric vessels on the duodenum. This pressure is merely a secondary result, even though there may be actual necrosis at the line of pressure. The condition appears to be one of the neuromuscular disturbances of the alimentary canal. When such a disorder takes the form of relative paralysis of the vagus with corresponding increase in sympathetic tone, the result is an obstruction characterized by great hypertrophy as well as dilatation. In acute dilatation of the stomach (and in acute paralytic ileus) both the sympathetic and the vagal systems of fibers are paralyzed and there is thinning of the dilated viscus. The paralysis is due to the shock of an abdominal operation or a severe injury such as an automobile accident, etc. It may be caused by toxins in acute peritonitis. The accumulation of gas is probably due to air-swallowing during general anesthesia. In the later stages a great outpouring of fluid, the so-called gastric succorrhea, serves to maintain the distension.

CHRONIC DUODENAL ILEUS

In this condition there is great dilatation of the duodenum, usually most marked in the third part, but sometimes in the first and second parts. The stomach is also dilated (Fig. 163), but the pylorus is not always involved. The condition is characterized by attacks of nausea with vomiting of bile.
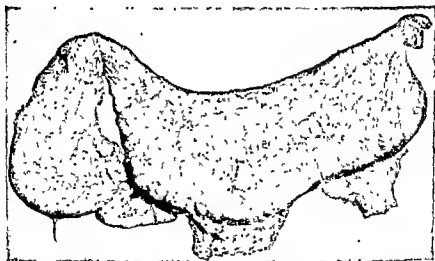
Fig. 163.—Chronic duodenal ileus. Enormous dilatation of stomach and duodenum.

The cause is usually regarded as being mechanical compression of the third part of the duodenum by the superior mesenteric vessels, this being aggravated by anything which produces a drag on the intestines. In support of this view is the fact that the dilatation may stop abruptly at the point where the mesenteric vessels cross the bowel. In other cases, however, no such relationship can be demonstrated, and it appears probable

that in the majority of cases the condition is neurogenic in origin due to an imbalance between sympathetic and autonomic impulses, and there-fore related to cardiospasm, Hirschsprung's disease, and other similar conditions. In many cases it will be found that the symptoms date back to childhood.

HOUR-GLASS STOMACH

In this condition the stomach is divided into two compartments, of which the pyloric is usually the smaller. It may, however, be as large as the cardiac half, in which cases there is danger of mistaking it for the whole stomach. Over 90 per cent of the cases are women.

The chief causes are: (1) a "saddle-shaped" ulcer on the lesser curvature extending on to both anterior and posterior walls, and pulling up the greater curvature in the process of contraction, with spasm also playing a part; the X-ray picture is striking (Fig. 164), (2) perigastric adhesions,

Fig. 164.—Gastric ulcer. Large crater on lesser curvature, with hour-glass contracture.

(3) carcinoma, (4) a congenital condition—very rare.

DUODENAL DIVERTICULA

Although the condition of diverticulum of the duodenum was described as long ago as 1710, its frequency has only been recognized as the result of recent X-ray studies. Some roentgenologists report the incidence as high as 1 or 2 per cent of the cases which they examine. Spriggs and Marxer in 1000 consecutive radiological examinations of the alimentary canal found duodenal diverticula 38 times.

The diverticulum varies in size from that of a pea to that of a small pear. In the larger specimens the opening is quite narrow. As in duodenal carcinoma, the common site is the second portion of the duodenum in the neighborhood of the ampulla of Vater (Fig. 165), then comes the first, and lastly the third portion. The diverticulum springs from the inner and posterior aspect of the bowel along the line of entrance of the vessels, a line of weakness where in other parts of the intestine, particularly the appendix, fat may be seen entering the wall and reaching the submucosa. Although usually single the diverticula may be multiple (Fig. 166). Like aneurism, it occurs in middle and later life. Rare cases, however, have been reported in infants.

The condition is in the nature of an aneurism. The mucosa and muscularis mucosae are protruded through the muscular wall, so that the wall of the sac is formed by these structures alone. The causes, therefore,

Fig 165.—Duodenal diverticulum. The white area to the left of the duodenal shadow is the diverticulum. Its connection with the second part of the duodenum is well shown.
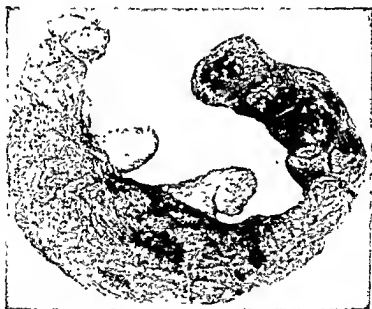
Fig 166.—Two duodenal diverticula. Both are in the second part of the duodenum.

although obscure and probably complex, are akin to those responsible for the production of an aneurism. Of these the two most important are weakening of the wall and increase of pressure within the bowel.

The weakness of the wall may be a congenital defect; it may be associated, in the case of the first part of the duodenum, with the presence of an ulcer; it may be due to traction from without from gall bladder disease; or it may be traced to the presence of rests of pancreatic tissue which are not infrequently found in the wall of the sac. The increase of pressure is attributed by Keith to enteroptosis and partial obstruction at the duodenojejunal junction.

Whilst usually discovered accidentally, the diverticulum may occasionally be accompanied by gastric symptoms, and when large may even give rise to obstruction.

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CHAPTER XIV

THE INTESTINES

In this chapter the more important pathological conditions affecting the intestine will be considered. The duodenum, the vermiform appendix, and the rectum are not included, the former having already been considered in connection with the stomach, and the two latter having special chapters devoted to them.

The surgical diseases of the intestines are many and varied, and it is difficult to group them into any convenient classification. They may, however, be considered under the following headings: (1) intestinal obstruction, (2) inflammations, and (3) tumors.

INTESTINAL OBSTRUCTION

The intestine is a hollow muscular tube the functions of which are the digestion of the food stuffs, their absorption after digestion, and the conveyance of unabsorbed matter to the rectum for expulsion from the body. The passage of the food along the tube is dependent on the muscular contractions of the bowel. These are of two varieties: (1) Rhythmic segmentation, a series of contractions by which the bowel is divided into a number of segments, which are at once broken up into other segments, so that the food is thoroughly mixed with the digestive juices without changing its position in the bowel. (2) Peristalsis, whereby the food is caused to move along the bowel, owing to contraction of the part immediately above the mass and dilatation of the part immediately below.

It is obvious that where obstruction of the bowel occurs from any cause these movements will be seriously interfered with. The peristaltic movements may become violent in their endeavor to force the contents past the obstruction, and the severe pain of intestinal colic will be felt. It is not yet certain whether this pain is felt in the bowel wall or is "referred pain" felt in the parietes. Normally the visceral peritoneum is insensitive, whereas the parietal peritoneum is exquisitely sensitive. The pain of early appendicitis is referred to the abdominal wall in the region of the umbilicus, as is that felt in strangulation of the small intestine. Whether the pain is referred in every case of intestinal disorder we cannot yet say.

There are many different classifications of intestinal obstruction, for which the reader is referred to Sir Frederick Treves' classical work. It is enough here to recognize two main divisions, the paralytic and the mechanical. In the *paralytic* form the intestinal tube is unable to pass on its contents, and the obstruction is as effective as if the lumen were blocked. The commonest and most important cause of intestinal paralysis is diffuse or localized acute inflammation. The *mechanical variety* may be due to a number of obstructive causes which will be taken up presently.

Intestinal obstruction may be acute or chronic. The former comes on with dramatic suddenness, sometimes with the rapidity of lightning,

whilst the approach of the latter is gradual and insidious. Frequently, however, in the last stages the chronic form suddenly becomes acute. The fundamental difference between the two forms is that in the acute variety the blood and nerve supply to the bowel is cut off, in the chronic it is not.

Acute Obstruction.—Acute intestinal obstruction is also known as acute ileus, because the ileum is the part of the bowel most often affected. The bowel is said to be strangulated, when in addition to the obstruction the vessels of the segment are also occluded. This can only occur in the mechanical form of obstruction. Simple obstruction without strangulation may occur as the result of impaction of a foreign body, *i. e.*, a large gallstone, or pressure of a fibrous band which does not occlude the vessels.

Causes.—The commonest cause of acute mechanical obstruction is strangulation of an external hernia. An internal hernia may also become strangulated. Such a hernia may occur (1) into the peritoneal fossae (duodenal, pericecal); (2) through the foramen of Winslow; (3) through openings in the mesentery or omentum which may be either congenital or traumatic in origin; (4) through the diaphragm (diaphragmatic hernia), the opening being congenital or traumatic. Other causes of acute mechanical obstruction are bands and adhesions, volvulus, and intussusception. Chronic obstruction, as from a tumor, may suddenly become converted into the acute form as the result of inflammation and edema. *Paralytic* ileus may be caused by acute peritonitis, severe intoxications, operations, external trauma, and mesenteric thrombosis or embolism.

Symptoms.—The chief symptoms of acute obstruction are vomiting, constipation, abdominal pain, and evidence of toxemia and dehydration. The stethoscope reveals loud splashing in acute obstruction; this is in marked contrast to the silent abdomen of acute peritonitis. The early symptoms such as pain, vomiting and shock are probably due to trauma to the sympathetic nervous system, while the later symptoms of collapse, dehydration and toxemia are due to the absorption of toxic products and associated biochemical changes. The vomiting is at first gastric (clear), later bilious, and finally stercoral (black and offensive). The higher the obstruction, the more fatal is the condition. Characteristic changes in the blood chemistry are hemoconcentration, high non-protein nitrogen and low chlorides. In high obstruction a severe degree of alkalosis is produced by the lowering of the blood chlorides due to the loss of hydrochloric acid from the stomach. The excess of base left in the blood combines with CO_2 to form bicarbonate. Dehydration due to the loss of fluid by vomiting probably plays some part in the fatal issue. The blood becomes correspondingly concentrated, so that the red cell count may rise as high as 10,000,000 per c.mm. The non-protein nitrogen of the blood may attain as high a level as in uremia. This is a point of great prognostic value, for if it continues to rise in spite of treatment the patient is going to die. It is due to increased formation from greater tissue breakdown, and in part to the dehydration.

Morbid Anatomy.—The classical example of acute obstruction is provided by a strangulated hernia, and the lesions will be described with this type in mind.

1. *Changes in the Strangulated Loop.*—The loop is paralyzed by

pressure on the nerves. Pressure on the veins causes marked engorgement of the small vessels, and there is exudation of serum and leucocytes into the wall of the bowel, so that it becomes thick and edematous. Rupture of the capillaries leads to petechial hemorrhages. The serous coat is purple in color, and its sheen is dulled by a fibrinous exudate. Occlusion of the arteries leads to gangrene, the loop becoming green and finally black. This part of the bowel is distended with fluid and gas. The fluid is partly due to the inflammatory exudate, but largely to an outpouring of secretion from the irritated intestinal glands. The accumulation of gas is due to a number of factors: (1) swallowing of air, (2) interference with the normal gaseous exchange between the lumen of the bowel and the veins, (3) putrefaction of the contents of the loop. At the actual site of the obstruction the pressure of the ring or band produces ischemic necrosis, as the result of which ulcers are formed in the mucosa. These may lead to perforation, even after the pressure has been relieved by operation.

2. *Changes Above the Obstruction.*—The proximal part of the bowel becomes acutely distended and is soon paralyzed. The distended coils are filled with fluid and gas, and the wall soon becomes inflamed, so that it assumes a purple color and is thick and edematous. Putrefaction of the contents occurs, and this leads to enteritis and the production of stereoral ulcers. At autopsy the degree of distension and the huge accumulation of fluid are sometimes quite remarkable.

3. *Changes Below the Obstruction.*—The distal part of the bowel is collapsed and empty. This is due to the initial violent peristalsis which occurs as the result of the strangulation. The empty condition of the bowel is sufficient explanation of the characteristic constipation, which can best be proved by the two-enema test.

The Cause of Death.—For years there has been unending controversy as to what it is that constitutes the danger in acute intestinal obstruction, especially in high obstruction. The simplest explanation was to assume that toxic products produced in the bowel above the obstruction were absorbed into the blood and caused the death of the patient. In 1912 Whipple and his associates found that when a loop of bowel is tied off in an animal it soon contains highly toxic split-protein products. Some workers believed that the toxins were formed from the intestinal contents, others that they were produced by the action of bacteria on the bowel wall. Undoubtedly the contents of the obstructed bowel are toxic, but only if they are injected into the test animal, not if they are administered by mouth or by duodenal tube. Moreover it has been demonstrated experimentally that when such toxic substances as histamine, strychnine or tetanus toxin are placed in the obstructed and strangulated loop they are not absorbed, at least in the earlier stages of the process. It becomes evident that the theory of toxic absorption from the bowel is inadequate.

In 1923 Haden and Orr showed that in experimental high obstruction profound changes take place in the composition of the blood. The chief of these changes are fall in blood chlorides, rise in non-protein nitrogen, increase in the carbon dioxide combining power, and blood concentration. The depletion of chlorides was supposed to be of fundamental importance, and was attributed to the continued vomiting with associated loss of

gastric HCl. For a time the popular treatment for the condition was the administration of sodium chloride and water, but such treatment made no impression on the high mortality. Death may occur before the chlorides are lowered to a significant degree. Moreover in the rabbit, which cannot vomit, there is the same chloride loss and dehydration as the result of acute obstruction. Again the popular theory had to be abandoned.

The present-day view is that the distension of the bowel is the most important factor and that the mechanism of shock is operative in the severe and fatal cases. This explanation is powerfully supported by the fact that treatment based on the theory has proved eminently successful. Taylor has shown by an ingenious technic that acute distension of the bowel without obstruction will produce the same symptoms as those of obstruction but without vomiting or change in the blood chlorides. The bowel was distended by means of a balloon which could be inflated, but obstruction was obviated by means of a large rubber tube attached to the balloon. Distension of the bowel wall is a powerful stimulant to secretion. The enormous amount of fluid in the shape of secretions, which in the course of twenty-four hours normally enters the upper part of the gastrointestinal tract and is absorbed in the lower part, is not generally appreciated; it amounts to between 5 and 7 liters daily. This amount is still further increased by acute distension of the bowel. It becomes evident that the loss of blood chlorides, blood concentration and resulting high non-protein nitrogen are not necessarily the result of vomiting, but are most likely due to great outpouring of fluid into the proximal part of the bowel with lack of absorption in the distal part. Decompression of the distended bowel by suction is the most valuable single method of treatment and has entirely changed the prognosis. Decompression can be effected by means of the duodenal tube, as suggested by Wangensteen or, even better, by the Miller-Abbott tube which is carried by the peristaltic action of the bowel to the level of the obstruction.

As the distension increases, the pressure within the lumen closes the veins, the arterial blood continues to be pumped into the bowel wall, and hemorrhage occurs from the capillaries and venules. The progressive anoxia results in necrosis, gangrene, and finally rupture. These changes are greatly aggravated by the presence of feces, which may act as a secretory stimulant. In experimental obstruction if the obstructed loop is first washed out it does not become gangrenous. Bowers stresses the paramount importance of distension in obstruction of the appendix, gall bladder, bladder and ureter, as well as the intestine.

Moon has emphasized the fact that acute obstruction resembles shock not only in some of its clinical features, particularly hemo concentration, but also in the postmortem picture. The essential basis of the condition of shock is a marked difference between the volume of the blood and the volume capacity of the vascular system. The syndrome may arise in different ways, one of which is decrease in the blood volume. We have seen that in high intestinal obstruction there is an enormous outpouring of fluid into the lumen of the bowel without accompanying absorption. At the same time the histological features of shock are observed postmortem, such as marked distension and engorgement of the capillaries and venules

in the viscera, edema and ecchymoses in the lungs and gastro-intestinal mucosa, and effusions into serous cavities. These lesions must be attributed to some toxic action on the capillaries.

The problem of shock is far from being solved, but for the present it seems reasonable to regard the process as follows: The obstruction causes violent peristaltic efforts and sudden distension of the proximal part of the bowel. This results in a tremendous outpouring of fluid, some of which is lost by vomiting, and none of which is absorbed. One of the most serious features of acute intestinal obstruction is loss of protein from the body. In simple obstruction without strangulation the loss is confined to plasma, so that hemoconcentration is a marked feature. When strangulation is present there is an added loss of red blood cells owing to damage to the vessels, so that the physiological disturbance is similar to that produced by massive hemorrhage. Modern principles of treatment take full cognizance of the importance of this protein loss. The protein content of the free peritoneal fluid is similar to that of plasma (Scott). In the later stages of strangulation, as the bowel wall becomes hopelessly damaged, bacterial invasion and absorption of toxic products, possibly related to histamine, may damage the capillary walls and allow still further escape of fluid.

Fig. 157.—Stercoral ulcers of bowel.

Chronic Obstruction.—This variety differs from the acute form in two important particulars: (1) the obstruction comes on slowly and insidiously, and (2) there is no interference with the vascular and nervous supply of the part. The obstruction may be due to the growth of a tumor (usually a carcinoma) in the wall of the bowel, to the gradual contraction of a band of scar tissue, or to pressure from without.

The effects of the obstruction on the bowel are those which might have been expected and foretold. Below the obstruction the bowel is collapsed and empty. Above, a varying degree of dilatation and hypertrophy takes place, hypertrophy especially in the small intestine, dilatation in the large. If the obstruction be *partial* hypertrophy is marked, owing to the active efforts of the bowel to force the intestinal contents past the obstruction. If it be *complete* the muscular contractions cease, there is paresis of the muscular coat, and the bowel above the obstruction undergoes passive dilatation. In the first case the result is a small cavity with thick walls, in the second a large cavity with thin walls. These principles may be applied to obstruction of any of the hollow viscera, the stomach, the intestine, the gall bladder, and the urinary bladder.

The distended bowel separates the two layers of the mesentery, so that shortening of the mesentery occurs, with fixation of the bowel.

So-called stercoral ulcers of the mucous membrane develop in the sev-

ment above the obstruction, owing to the irritation of the hard scybalous masses which collect there (Fig. 167). A certain amount of catarrhal inflammation develops in consequence, with the result that there may be periodic attacks of diarrhea with the passage of semi-fluid matter mixed with mucous. Attacks of diarrhea alternating with periods of constipation are thus always highly suggestive of chronic obstruction.

The common causes of intestinal obstruction, acute or chronic, are (1) carcinoma; (2) adhesions, bands, and cicatrices; and (3) inversions and torsions.

CARCINOMA

The common sites of cancer of the bowel, when the rectum is excluded, are the pelvic colon and the cecum. The next most frequent positions are the ascending colon, the splenic flexure, and the hepatic flexure. Cancer of the small intestine is of very rare occurrence.

Fig. 168.—Carcinoma of bowel of the fungating type.

The growth commences in the mucous membrane as an adenocarcinoma. The appearance varies with the mode of growth. (1) The tumor may project into the lumen as a fungating, cauliflower-like mass which speedily becomes ulcerated, with the usual addition of symptoms of toxemia to the clinical picture (Fig. 168). The typical microscopic appearance of adenocarcinoma is well maintained. This form is common in the cecum.

Or (2) the carcinoma may infiltrate the bowel wall rather than project into the lumen. An annular growth is formed around the gut, which is comparatively poor in epithelial elements but rich in fibrous tissue, so that the tumor is a scirrhus such as has already been studied in the pylorus of the stomach. The contraction of the fibrous tissue causes narrowing of the lumen much more extreme than that produced by the previous variety; and in many cases it looks as if a tight string had been tied around the bowel, the actual tumor being of quite small dimensions. This is the usual form in the pelvic colon. Ulceration is late. The proximal part of the bowel may become greatly dilated (Fig. 169), and the fecal accumulation is apt to cause enteritis and the formation of stercoral ulcers. This is the basis for the attacks of diarrhea which may alternate with the constipation which is so characteristic.

In both forms mucoid degeneration is not uncommon. Indeed it is

more frequent in the intestine than in the stomach. Care must be taken not to make a mistake in the microscopic diagnosis, for in some sections the appearance may be merely that of mucoid degeneration, not an epithelial cell being visible.

Spread.—Spread is slow, especially in the distal colon. It takes place (1) by direct infiltration, (2) by the lymph stream, and (3) at a late date by the blood stream.

1. *Direct Infiltration.*—The tumor cells first spread in the submucous coat. They tend to encircle the bowel, giving the annular form of car-

Fig. 169.—Carcinoma of large intestine, with extreme dilatation above the obstruction.

cinoma. In time they penetrate the muscle and the serous coat and appear on the surface. They may be sown over the peritoneum of the pelvic floor, and becoming implanted on the ovaries, give rise to secondary tumors of large size. The tumor may become adherent to the bladder, coils of small intestine, and other adjacent structures.

2. *Lymph Spread.*—The tumor cells do not pass quickly to the regional lymph nodes, so that cancer of the large bowel is one of the less malignant forms of carcinoma. It is commonly stated that lymph spread is commoner and earlier in cancer of the cecum than in cancer of the descending colon and sigmoid, as the cecum, which is more concerned

with absorption, is better supplied with lymphatics. Autopsy statistics, however, show that lymph-borne metastases are even more common on the left side than on the right (Mayo and Schlicke). The glands draining the proximal colon lie along the ileocolic artery, those draining the distal colon are found along the branches of the inferior mesenteric artery. The traverse colon drains into glands in the mesocolon.

3. *Blood Spread.*—This usually occurs only in the end stages, but may sometimes take place when the primary growth is still small. Metastases occur first in the liver owing to spread by the portal vein. More rarely the other viscera may be involved.

The late *symptoms* of carcinoma of the large bowel are easily explained on a pathological basis. With the stenosing type there is obstruction and the production of ribbon-like stools. In the fungating type there is hemorrhage from the soft friable surface, and later, when ulceration occurs, there may be foul stools, alternating diarrhea and constipation, and cachexia. But, as Scrimger has insisted, many of these symptoms merely indicate an inoperable condition, and are of interest for prognosis rather than diagnosis. The appearance of blood in the stool is an early sign io cancer of the rectum, but a late sign in cancer of the sigmoid. The operable cases give a history of rather persistent constipation accompanied by occasional attacks of colicky pain, which gradually become more frequent and may culminate in acute obstruction. It sometimes happens that the first indication of carcinoma is the development of acute intestinal obstruction due to inflammatory swelling and edema at the site of the stricture. Amongst the earliest symptoms is a change in the habitual action of the bowels, sometimes associated with abdominal discomfort. Anemia is common in cancer of the cecum. In this region of the bowel acute ileus and even marked obstruction are rare owing to the liquid nature of the stool, and for the same reason a succussion sound is characteristic of dilatation of the cecum. In the transverse and descending colon early obstruction (chronic) is common.

ADHESIONS, BANDS, AND CICATRICES

There is a multiplicity of ways in which bands in the abdomen may cause strangulation of the bowel.

In an *ordinary hernia* an additional knuckle of bowel may slip through the inguinal or femoral ring, and become constricted by the unyielding margin of the ring. Or a *retroperitoneal hernia* may occur into one of the peritoneal pouches, of which the principal are the *paraduodenal fossa*, situated on the left side of the ascending part of the duodenum with its left border formed by the inferior mesenteric vein; the *mesentericoparietal fossa*, of which the anterior boundary is formed by the superior mesenteric artery; the fossae in the neighborhood of the *ileocecal* junction notably the *ileo-appendicular* and the *retrocolic*; and in rare cases there may be a hernia into the foramen of Winslow and other unusual sites.

Peritoneal adhesions are a not uncommon cause of intestinal obstruction. Owing to some previous attack of inflammation a fibrous band is formed which stretches from the wall of the bowel to some fixed point, and by gradual contraction may pull upon the bowel to such an extent

as to produce kinking and obstruction. In these cases there is no sudden obstruction to the blood supply of the part, and the symptoms are therefore less catastrophic in nature.

Obstruction may be produced by abnormal bands of peritoneum or omentum, by a *Meckel's diverticulum*, or by an *appendix* or *Fallopian tube* which has become adherent to the parietes.

INVERSIONS AND TORSIONS

Intussusception.—Rutherford Morison remarks that the tendency to turn inside-out seems common to all of the hollow viscera. It is most frequently met with in the intestine, and at least 75 per cent of the cases occur within the first year. Of these about 70 per cent are in boys.

The effect of intussusception depends on whether there is interference with the blood supply. If there is, the symptoms will be those of acute obstruction and strangulation; this is what usually occurs. If there is not, the condition is more or less chronic.

By far the commonest position is the ileo-cecal junction (Fig. 170). This is because local inflammation and other sources of irritation are common in this position, and the disparity in size between the small and the large intestine favors the production of the condition. The inversion may occur at other parts of the bowel, especially if a polypus happens to be projecting into the lumen. Indeed innocent tumors of the bowel derive much of their importance from their tendency to predispose to this accident.

The muscular contractions of the sheath soon produce venous congestion and swelling of the contained part, the two layers of which become adherent to one another owing to the inflammation which rapidly supervenes. Blood is effused into the wall and lumen of the bowel, and is discharged, mixed with mucus, from the rectum.

Fig. 170.—Intussusception at ileo-cecal junction.

As the intussusception progresses along the large intestine it assumes a curved, sausage-shaped appearance, owing to the traction of the mesentery attached to the promontory of the sacrum. Twisting of the mesentery is naturally liable to occur, in which case symptoms of acute strangulation rapidly supervene. Bacteria invade the walls of the bowel, so that gangrene is the next step. This involves the entering and returning portions, but seldom the sheath. The prognosis depends entirely on the

rapidity with which a correct diagnosis is made and appropriate treatment carried out.

In the course of an autopsy small intussusceptions, frequently multiple, are often observed in the small intestine. These are agonal in nature, being produced by the irregular spasmodic contractions at the time of death. They are readily recognized though presenting no signs of inflammation, and being readily reduced.

Volvulus.—Torsion is an accident to which many of the abdominal organs are liable—the intestine, the gall bladder, the kidney, the spleen, the testicle, the uterus (especially when the seat of fibroids), an ovarian cyst, a hydrosalpinx or pyosalpinx, etc. Of these torsion of an ovarian tumor is the commonest, whilst the intestine comes next in frequency.

The causes of volvulus are obscure. Chronic constipation and congenital or acquired defects in the mesenteric attachment probably play an important part. The actual twisting may be brought about by irregular peristaltic contractions, or a physical factor such as the weight of the distended bowel may be the exciting cause. The pelvic colon is much the commonest site of the accident.

The result of the twisting is to produce strangulation and acute obstruction, owing to occlusion of the vessels in the mesenteric attachment, first the veins and then the arteries. The effect is first extreme venous engorgement, and then gangrene of the bowel.

INFLAMMATORY CONDITIONS

The intestine may be the seat of a variety of inflammatory affections. Of these the most important are tuberculosis, typhoid fever, dysentery, chronic ulcerative colitis, and regional ileitis. Secondary inflammations, such for instance as the stercoral ulcers produced by accumulations of fecal masses, have already been considered. The lesions of typhoid and dysentery are more properly discussed in works on medicine. Tuberculosis, chronic ulcerative colitis and regional ileitis will be taken up here.

TUBERCULOSIS OF THE INTESTINE

Tuberculosis of the bowel occurs in two forms which are so distinct from one another that they will be described separately. These are (1) the ulcerative variety, (2) the hypertrophic variety.

Ulcerative Tuberculosis.—Ulceration of the bowel due to tuberculosis usually occurs in children or in young adults. The common site is the lower end of the ileum, but the ulcers may be scattered over a considerable length of the bowel, involving either the lower end of the small intestine or the commencement of the large intestine, or both (Fig. 171).

This, at least, is the result of pathological investigation conducted in the autopsy room. Recently, however, the ulcerative variety of intestinal tuberculosis has been attracting the attention of surgeons, and the findings of the operating room differ somewhat from those of the autopsy room. In the former the early stages are seen, in the latter only the end picture. The work of Archibald and others has shown that the disease commences in the cecum, and spreads from there both up and down the bowel. This progress was well seen in a number of cases in which a second laparotomy was done some months later. In the majority of Archibald's cases the

cecum was easy to palpate, whether the small bowel or the rest of the colon was involved or not. The remainder of the colon may show isolated ulcers, but is rarely involved so extensively as to be palpable. The limits of the disease can be recognized at operation from the tell-tale signs enumerated below.

The infection may be primary, due to ingestion of the bacilli in tuberculous milk, a method common enough in children but very rare in adults; or it may be secondary, due to the swallowing of tuberculous sputum. It is as a complication of pulmonary tuberculosis that tuberculosis of the bowel acquires its great importance.

The frequency of the condition is much greater than used to be suspected. During a period of four years, 37 per cent of tuberculous patients admitted to the Manitoba Sanatorium were suspected of intestinal ulcer-

Fig. 171.—Tuberculosis of intestine. Caseous masses are seen in base of ulcer and in adjoining submucosa. ×30.

ation, and of 300 suspicious cases investigated 50 per cent were found positive and 20 per cent doubtful (Pritchard). It is well to remember that general symptoms usually occur before local symptoms. The presence of tubercle bacilli in the stools is of no diagnostic significance unless the sputum is negative or absent.

The lymphoid tissue in the Peyer's patches and solitary glands is the first to be infected, but the disease differs from typhoid in that it does not remain confined to these structures, but spreads along the wall of the bowel, often in an encircling manner so as to give rise to "girdle ulcers." The edges of the ulcers are ragged, irregular, and often undermined, whilst the floor is covered with small tubercles. The position and nature of the ulcers can be recognized from the outside, the wall is thickened and the peritoneal coat congested at the spot, and minute grey tubercles or a

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patch of reactive fibrino-plastic exudate may betray the position of the underlying ulcer. Enlargement of the lymphatic glands, with or without caseation, is common.

Adhesions to surrounding parts are common, and this, together with the inflammatory thickening of the serous coat which is commonly present, renders perforation an uncommon accident.

The great surgical importance of ulcerative tuberculosis lies in the fact that healing is followed by cicatricial contraction which, on account of the encircling form of the ulcer, may give rise to a marked degree of obstruction. As the ulcers are often multiple, there may be several points of stricture, the intervening segments showing a dilatation and sacculation which is quite characteristic. A commoner cause of obstruction is kinking of the bowel due to the adhesions which are described in connection with tuberculous peritonitis.

Fig. 172.—Hypertrophic tuberculosis of cecum.

Hypertrophic Tuberculosis.—In this condition the formative are in excess of the destructive processes. It always commences in the ileo-cecal region, although it may spread upwards along the ileum and downwards along the cecum. It occurs in young adults, and is rare over the age of forty.

There is great formation of tuberculous granulation tissue, similar to that which is found in tuberculous synovial membranes, mainly in the submucous but to some extent also in the subperitoneal coat. Giant cells are abundant but miliary tubercles are not common, and caseation is usually absent.

Owing to the formation of new tissue in the submucosa, the mucous membrane is folded and nodular, and projects into the lumen in the form of small papillomatous masses (Fig. 172). Ulceration may develop, but is not a marked feature of the condition. The mucosa may gradually encroach upon the lumen until extreme narrowing results, so that it may only be possible to pass a fine probe through the opening.

The affected part of the bowel is thickened and stiff, and may form a tumor-like mass which may bear a strong resemblance to a carcinoma even after the abdomen has been opened. The neighboring lymphatic glands are usually enlarged, thus still further adding to the mass which is felt through the abdominal wall. The more diffuse nature of the thickening and the younger age of the patient are points in the differentiation from carcinoma.

REGIONAL ILEITIS

In 1932 Crohn and his associates described a disease of the terminal ileum affecting mainly young adults, characterized by a subacute or chronic necrotizing and cicatrizing inflammation, and associated with ulceration of the mucosa and very marked fibrosis which may cause great narrowing of the lumen. To this condition they gave the name terminal ileitis, but as it is now known that the lesion need not be confined to the terminal part of the ileum it is called regional ileitis or regional enteritis.
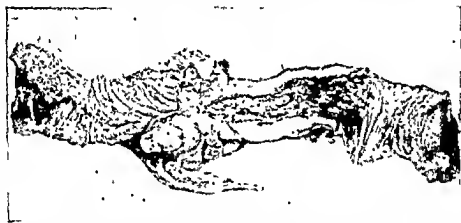
Fig. 173.—Regional ileitis. The lower part of the ileum is markedly thickened and the lumen narrowed. (Kindness of Dr. Paul Klemperer.)

It is also known as Crohn's disease. In some cases the colon has been involved.

The wall of the affected segment of bowel is thickened and rendered rigid to such a degree that it resembles a hose-pipe (Fig. 173). A mass can therefore be felt, usually in the right iliac fossa. The serous surface is reddened. The condition frequently begins abruptly at the ileo-cecal valve, and tapers off as it ascends the ileum for a distance of 8 or 12 inches. The submucosa shows marked inflammatory changes and is infiltrated with polymorphonuclears, lymphocytes and plasma cells. The thickening may be so extreme that the lumen of the bowel will admit only a medium-sized probe. Necrosis and destruction of the mucosa occur later. The regional mesenteric lymph nodes are frequently enlarged. Both the mesenteric lymphadenitis and the ileitis are apparently due to some low-grade infection. The condition is usually mistaken for appendicitis. When ulceration occurs the clinical picture is that of ulcerative colitis, with diarrhea, cramp-like abdominal pain, and sometimes blood and mucus in the stool. Ulceration is followed by stenosis, and the picture now

becomes one of obstruction. Finally multiple fistulas may develop, opening into the colon or on to the abdominal wall. Excellent color plates of the lesions will be found in the paper by Barrington-Ward and Norrish.

CHRONIC ULCERATIVE COLITIS

This disease is in part surgical, so that it may be considered here. It is an extremely chronic infection with acute exacerbations, which is characterized by diarrhea, with blood, pus and mucus in the stools. These, of course, are the symptoms of dysentery, whether amebic or bacillary. Secondary anemia and loss of weight are common. The roentgen rays show a hyperactive colon with loss of the normal haustrations (pipestem colon). It is with the sigmoidoscope that the diagnosis can be made with ease and certainty. Hurst remarks that just as no one would diagnose and treat tonsillitis without looking at the tonsils, so no one should diagnose and treat ulcerative colitis without looking at the colon with the sigmoidoscope. When this is done the bowel is seen to be hyperemic, and numerous ulcers are scattered over the mucosal surface. When the mucus which covers the surface of the ulcers is wiped away many fine red spots become apparent, from which bleeding takes place at the slightest touch.

Fig. 174 —Ulcerative colitis. The ulcers are separated by bridges of mucosa.

The etiology is obscure. There are two ways of regarding the condition, both of which have strong supporters. According to the first the disease is a specific infection due to a single bacterial agent, probably a bacillus of the dysentery group. The acute lesions are practically indistinguishable from those of bacillary dysentery, and B. dysenteriae has been cultured from the base of the ulcers. By some it is thought that the infection is caused by a specific diplococcus resembling the pneumococcus (Bargen). The second view is that the condition is a specific reaction to a number of influences which can initiate muscular spasm in the colon. Such influences include dysentery, vitamin deficiency, and possibly hyperactivity of the parasympathetic system. In one case of spinal cord injury which I observed the patient developed acute ulcerative colitis before he died. Spasm of the colon produced experimentally in a variety of ways causes damage to the epithelium and ulceration. The ulcers occur principally over the taenia coli, where spasm is most marked. "Once the colon becomes spastic, it is potentially an organ that can produce severe damage to its own surface structures" (Lium).

The active lesions are ulcers which are usually confined to the colon and rectum. They may be most marked along the taenia coli. In severe cases the entire lining of the large bowel may be a mass of ulcers of every size and shape (Fig. 174). They are usually quite superficial, often mere

erosions, but the muscular coat may undergo necrosis, so that the base of the ulcer is formed only by peritoneum with imminent danger of perforation. The intervening mucosa is often swollen and edematous so that polypoid masses project from the surface (colitis polyposa). One of these polypi may become malignant. The wall of the bowel is often very friable, so that the sigmoidoscope has to be used with care. *Microscopically* the mucosa has disappeared over the ulcers, and the submucosa is infiltrated with round cells and leucocytes. Between the ulcers the mucosa is thick, extremely congested and edematous. *Healing* occurs with very little scarring, so that stricture of the bowel is not a complication.

FECAL FISTULA

A fecal fistula is an abnormal track by means of which the lumen of the bowel communicates with the skin surface, bladder, vagina, or another loop of bowel. It may be due to many causes, of which the chief are (1) perforating wounds of the abdomen and (2) the development of an abscess which establishes a communication between the bowel and the skin, etc.

The length of the fistula depends on whether the bowel has become adherent to the abdominal wall before the formation of the fistula. Suppuration in the neighborhood of the appendix is one of the commonest causes. In such a case the fistulous track will be lined by granulation tissue, and pus will be present in the discharge. In one of our cases perforation of the bowel with the establishment of a fistula was due to pressure from a rubber drainage tube.

The part of the bowel involved may be indicated by the nature of the discharge. If the latter is acid in reaction, contains bile and undigested food, and produces irritation of the skin, the upper part of the jejunum is probably involved. If it is alkaline in reaction, and contains no recognizable bile or undigested food, the opening is probably into the lower part of the small intestine. If it is fecal in odor, semi-fluid in consistence, and contains mucus, the fistula communicates with the cecum. If the contents are almost solid and evidently fecal, the lower part of the colon is implicated.

INTESTINAL DIVERTICULA

Radiological studies have shown that diverticula of the intestine are of much more frequent occurrence than was formerly supposed to be the case. The presence of diverticula of the large bowel, the condition known as diverticulosis, was found in 100 out of 1000 consecutive radiological examinations of the alimentary canal made by Spriggs and Marxer. Mailer reports that at the Mayo Clinic in 1925 diverticula were found in 5 per cent of radiological examinations of the colon, and in 7 per cent of autopsies. The condition is therefore a common one.

We may recognize three different stages in the process of diverticulosis: first, the prediverticular state, second, the formation of diverticula, and third, inflammation or diverticulitis. The radiological characteristics of the prediverticular state were first described by Spriggs and Marxer. The affected segment of bowel is spastic and fails to dilate, it does not show the normal segmentation, and its outline is ragged. At later stage the bowel shows an irregular segmentation, broad and deeply serrated,

Fig. 175.—The descending colon and sigmoid show an early condition of diverticulosis. The "spiking" is well shown.
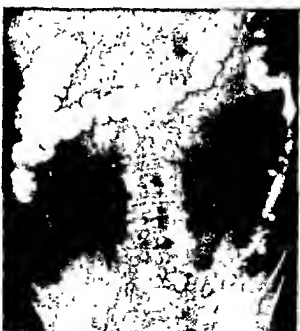
Fig 176 —Diverticulosis of descending colon and sigmoid.

and may present a characteristic "spiked" or "saw-toothed" appearance (Figs. 175 and 176). By this time the little pockets of developing diverticula may be seen.

Seymour Barling has described what must have been a very early stage of the process as observed during the course of a laparotomy. The bowel suddenly narrowed at one point till it was no thicker than the index finger, it became extremely rigid, and while the spasm lasted tiny saccules appeared between the longitudinal bands, lying like beads along the sides of the gut. In a few seconds the spasm passed off, and the tiny projections could no longer be seen.

Spriggs has shown that the differentiation of diverticulosis from diverticulitis can be made by means of serial X-ray studies. When inflamma-
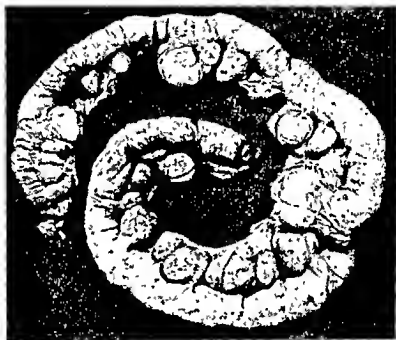
Fig. 177.—Multiple diverticula of the small intestine. An unusual form, in which the diverticula started at the pylorus and extended down the small bowel for a distance of 5 feet. (Courtesy of Dr. James Prendergast.)

tion has occurred in the diverticula the normal peristaltic waves are lost, as can be demonstrated by superimposing one picture upon another and taking tracings. Efficient medical treatment may avert indefinitely the onset of these secondary changes. Once the diverticulitis is established, however, it always appears to be progressive.

It may appear a matter for wonder that diverticula, which are now encountered with comparative frequency, should have been so completely overlooked in the past, even by morbid anatomists of wide experience. The reason is twofold: (1) the diverticula are small and are usually buried in fat; (2) the secondary pathological changes presently to be described tend even more effectually to cover up the diverticula.

The diverticula may occur at any period of life, but they are more com-

mon in middle and late life. They are extremely rare before the age of thirty.

In the small intestine the diverticula occur along the line of the mesenteric attachment (Fig. 177), because it is at this point that the vessels pierce the bowel wall, often carrying in with them a sheath of fat, and thereby constituting a *locus minoris resistentiae*. In the large intestine, on the other hand, they are situated along the convexity rather than the concavity of the gut, frequently in two rows (Fig. 178A) and almost always multiple. The rows are commonly situated along the edge of the longitudinal muscle bands, but the diverticula may occur in any position be-

Fig. 178.—Diverticulosis. A, Outer aspect. B, Inner aspect.

tween these bands, or opposite the mesenteric attachment, and it is not uncommon to find one or more of them passing into an appendix epiploica.

The average size of the diverticula is that of a large pea, but they vary from microscopic dimensions up to the size of a plum stone. The greater number are sessile, but some may be pedunculated. The opening into the intestinal lumen varies much in diameter (Fig. 178B); in some cases the opening is so small as to constitute a real stenosis. The contents consist of fecal matter; hard concretions may be present. In the small intestine the contents are fluid. There can be little doubt that the difference in the contents of the diverticula explains why the lesion in the small intestine should almost never be accompanied by symptoms, whilst in the large intestine pathological complications are frequent.

The diverticula are sometimes divided into the congenital and the acquired. It is probable that the acquired depend upon an original congenital weakness of the intestinal wall. The congenital class is due to some embryological defect; Meckel's diverticulum is a good example.

Another subdivision is into the complete and the incomplete. In the complete the sac is formed of all the layers of the intestinal wall. In the incomplete or false diverticula, which are by far the commoner, the sac is formed of mucosa, submucosa, and serosa. It is indeed a hernia mucosae through a weak point in the muscular coat (Fig. 179).

Etiology.—The etiology of diverticula formation is not certain. McGrath, as the result of a combined anatomical and experimental investigation, came to the conclusion that no single factor was enough to explain the origin of ordinary diverticula. As in the case of an aneurism or a hernia.

Fig. 179.—Diverticulosis. The mucous membrane is being extruded through the muscular wall.

the fundamental factors are insufficient resistance of the wall and increased pressure from within. The cause of the weakening of the wall is undecided. There are those who attribute it to a congenital defect. This appears improbable, as diverticulosis is very rare before middle age. An inflammatory process the result of infection may play an important part, as suggested by Spriggs and Marxer, but Mailer could find no evidence in support of this in his material. It appears most probable that the weakness is degenerative in character, due to the loss of tone and elasticity of muscle which is characteristic of the degenerative period of life. Chronic constipation can hardly play an important part, otherwise the condition would be more common in women than in men, whereas the reverse is the case. During peristalsis a wave of relaxation precedes the wave of contraction. It has been suggested that a relaxed segment may be caught between two

contracting segments, and a herniation started in this way. Such protrusions have been observed at operation. Possibly neuromuscular imbalance may be responsible.

Diverticulitis.—Diverticula in themselves are innocuous. The trouble lies in the fact that fecal matter is constantly being pushed into them, and because there is a lack of muscle in the wall of the sac this material tends to remain imprisoned, especially when the neck of the sac is narrow. The feces become inspissated and form a fecolith, the constant pressure of which on the mucosa starts infection. Infection may lead to an inflammatory condition of diverticulitis which may be either acute or chronic.

Fig. 180.—Peridiverticulitis. Numerous areas of inflammation in the fatty tissue around the bowel.

The *acute changes* are quite analogous to what is seen in the appendix. As the result of the presence of a hard concretion irritation is set up, the effect of which may vary from a slight abrasion of the mucosa to perforation resulting in general peritonitis, local abscess formation, or fistulous communication with other viscera or with the abdominal wall. Perforation of a diverticulum is a comparatively frequent occurrence, and may be the first indication that there is anything amiss. Often, however, the surrounding adhesions are sufficient to ensure that the perforation will do no more than result in a local abscess. The symptoms may naturally closely simulate those of acute appendicitis, except that the lesion is on the left side of the abdomen.

Equally important are the *chronic results* of infection, to which Wilson has given the name of *peridiverticulitis*. This is a condition of chronic extramucosal inflammation (Fig. 180), the result of a leakage of toxins or bacteria through the mucosa, with the formation of a large mass and not infrequently the production of stenosis. It is obvious how readily such a condition may be mistaken for carcinoma. Even at operation the mistake is readily made, for the diverticula are completely buried in the dense inflammatory mass.

Many of the cases of spontaneous cure of cancer of the sigmoid, with or without the aid of Christian Science, were doubtless examples of this condition. In his excellent paper on the subject Telling remarks: "Of all the secondary results this proliferative inflammation is the most important, the most frequent, and probably the most overlooked." The resected mass consists of a large amount of fat and dense fibrous tissue. Microscopically it is made up of granulation tissue containing an abundance of the fixed connective tissue cells. Giant cells may be met with, and these must not give rise to a mistaken diagnosis of tuberculosis. When the lumen is opened the mucosa is found to be intact, but small pits with edematous margins are seen; these are the openings of the diverticula into which a probe may be passed. In order best to demonstrate the diverticulum McGrath recommends that thin slices should be cut from the external surface of the mass; when the opening of a diverticulum is encountered a probe can be passed into the lumen of the bowel.

Relation to Carcinoma.—Some authors believe that a causal relationship exists between diverticulitis and carcinoma. My own experience does not support this view. It seems more probable that when the two are associated it is merely a coincidence. A simple method of differentiating in the gross between carcinoma and diverticulitis has evidently been usually overlooked in the past, considering how frequently diverticulitis has been mistaken for carcinoma, and that specimens of the former disease have even found their way into museums labelled as the latter. In diverticulitis there is practically never any ulceration or involvement of the mucous membrane; in carcinoma this is extremely frequent.

Meckel's Diverticulum.—The vitelline duct or yolk stalk which connects the yolk-sac with the intestine is obliterated early in intrauterine life and the fibrous cord into which it is converted becomes incorporated with the umbilical cord, so that it passes to the umbilicus. In about 3 per cent of cases that part of the yolk stalk which lies between the intestine and the umbilicus fails to degenerate, and remains patent. As a rule it is only the proximal part which remains open. This forms a pouch-like projection which arises from the lower end of the ileum, usually within two feet of the ileo-cecal junction. The projection may be a mere dimple, or it may extend as far as the umbilicus, thus forming an umbilical fistula through which feces may escape. The pouch is generally quite short, is continued as a fibrous band which may be adherent to the umbilicus, or may form some new attachment to the mesentery of the ileum or a loop of intestine. Heterotopic gastric mucosa is not infrequently present in the diverticulum; heterotopic pancreatic tissue is n good deal rarer.

Complications.—(1) The communication between the diverticulum and the intestine may become closed, with the formation of a cyst filled with

mucoid material. (2) Acute inflammation may supervene, especially when the opening is narrowed; the symptoms are those of acute appendicitis. (3) When the cord-like termination of the diverticulum becomes adherent to some neighboring structure an opening is formed through which an internal hernia may be formed with possible strangulation. (4) A volvulus may be produced by the weight of a large diverticulum distended with fecal material, causing acute intestinal obstruction (Fig. 181). (5) A peptic ulcer may develop, especially in children, owing to
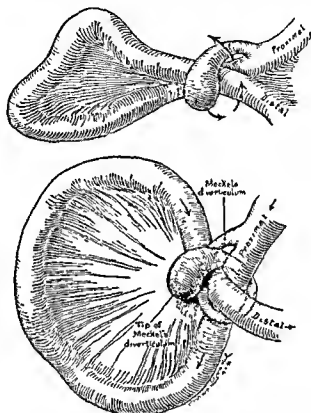
Fig. 181.—A diverticulum tying off a loop of small bowel. This indicates the manner in which the obstruction occurred. Meckel's diverticulum has dropped over a loop of bowel which has been partly twisted. After passing under the loop it curves upward and passes through the space between the base of the diverticulum and the adjacent small bowel. With the consequent distension of the constricted bowel, complete obstruction has resulted. (Cullen.)

the presence of heterotopic gastric mucosa in the diverticulum (Fig. 182). Such an ulcer is liable to the same complications as a gastric ulcer, namely hemorrhage and perforation. This is one of the uncommon causes of passage of blood from the bowel.

Developmental Enterogenous Cysts.—All cysts in the abdominal cavity having the structure of the gut are developmental in origin. They may develop in the vitello-intestinal tract (between the gut and the yolk-sac), or in diverticula of the developing entoderm which may persist in adult life. The usual site is the ileocolic angle. The cyst

may be (1) in the wall of the bowel, (2) attached to the serous coat, or (3) remote from the bowel. The wall may consist of muscle, submucosa and mucosa. The lining shows great variety of structure, due to intracystic pressure and inflammatory change. The epithelium may be stratified, cylindrical or atrophic.
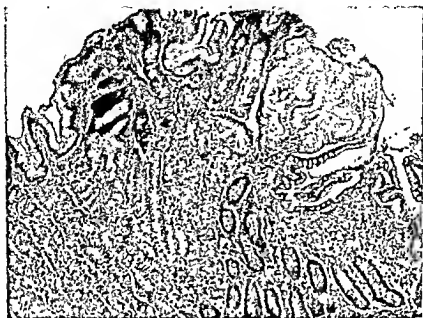
Fig. 182.—Gastric mucosa (on left) in Meckel's diverticulum. × 50.

HIRSCHSPRUNG'S DISEASE

This rare condition, known also as congenital dilatation of the colon and megacolon, is characterized by great dilatation and hypertrophy of the colon unaccompanied by any organic or spasmodic obstruction. It is much commoner in boys than in girls. The abdomen is greatly and uniformly distended (Fig. 183). Although the condition is congenital, the onset of symptoms may be long delayed. It is progressive and usually ends fatally.

Etiology.—There is no evident obstruction at the anus or at the pelvi-rectal junction to account for the remarkable dilatation, but there appears to be what may be called a neuromuscular obstruction. In other words, there is a defect in the co-ordinating mechanism of the musculature of the lower part of the colon and rectum. The condition belongs to the same group as cardiospasm, spasmodic obstruction of the pharynx, and other examples of what has been called achalasia, a term which indicates that the essential defect is an inability of the sphincter to relax rather than a true spasm. The colon and rectum have a double nerve supply from the autonomic nervous system. The circular muscle is supplied by sympathetic fibers arising from the lumbar rami communicantes and passing down through the sympathetic trunks and the hypogastric and pelvic plexuses. The longitudinal fibers are supplied by the parasympathetic. Hyperactivity of the sympathetic innervation to the pelvirectal junction leads to a condition of increased tone of the sphincter which

makes it impossible for it to relax; it is an example of neuromuscular obstruction. Although it is not possible to demonstrate an anatomical sphincter at the lower end of the sigmoid, there can be no doubt that there is a physiological mechanism at the pelvirectal junction which keeps the rectum empty except during defecation. In support of this theory is the great relief afforded by lumbar sympathectomy, the object of which is to reduce the sympathetic stimuli and lessen the tonus of the circular muscle.
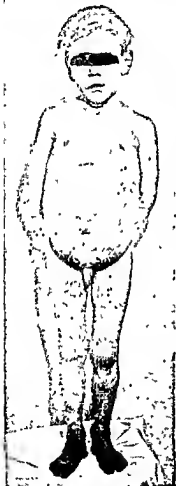
Fig. 183.—Hirschsprung's disease.

Morbid Anatomy.—The lesion is generally confined to the colon. The sigmoid is most affected and is often the only part involved. The process tends to extend proximally, so that the descending, transverse, and ascending colon and finally the cecum may be implicated. In rare cases the lower part of the ileum may be involved, a condition of mega-ileum. The lesion usually ends at the junction of sigmoid and rectum, but sometimes the rectum is involved to a minor degree. There is a combination of dilatation and hypertrophy. The dilatation may be enormous, so that the pelvic loop of the colon, which resembles a flexed leg and thigh and may measure 8 inches in diameter, may come to occupy the entire abdomen and cause extreme distension. The wall may be half-an-inch thick, the hypertrophy involving the mucous and submucous coats as well as the extremely thick circular muscle coat. The taenia coli are less marked than usual. The great hypertrophy is an indication of the efforts which the dilated bowel makes to empty itself. The serosa is thick and roughened. The lumen is filled with liquid feces and scybalous masses, but much of the distension is due to gas. The mucosa may be ulcerated and always shows catarrhal inflammation. It is said that there may be changes in Auerbach's plexus in the bowel wall, but too much stress should not be laid on these as they may well be secondary. It is probable that the neuromuscular disturbance is central rather than peripheral in origin.

There is an *acquired* form of megacolon. It is usually seen after the age of 50, and is limited to the pelvic colon. It appears to be the result of a chronic form of volvulus, so that the hypertrophy and dilatation are due to mechanical obstruction.

Lesions of the Appendices Epiploicae.—The appendices epiploicae are found along the length of the large bowel. They represent peritoneal pouches containing a varying

amount of fat. The chief pathological conditions to which it is liable are (1) torsion, (2) acute inflammation, (3) detachment, and (4) the formation of adhesions. All of these are rare. (1) When *torsion* occurs the appendage may become strangulated owing to interference with the blood supply. The accident is commoner on the right side, so that the condition is likely to be mistaken for acute appendicitis. The cause of the torsion is not certain. It usually affects an appendage which is abnormally long and loaded with fat. As a result of the torsion the appendage may become separated. (2) *Acute inflammation* is due to infection. This is more uncommon than torsion. The appendage may become gangrenous. The clinical picture is that of acute appendicitis when on the right side, acute diverticulitis when on the left. (3) *Adhesions* may be formed between an appendage and the parietes or a neighboring viscus. Acute intestinal obstruction may be caused by the fibrous band. (4) *Detachment* gives rise to the presence of a foreign body in the abdominal cavity. When this follows acute torsion it is easy to understand, but it may occur without any acute symptoms. In an appendage which is loaded with fat there may be slow obliteration of the vessels, with necrosis of the base and finally detachment. The free body resembles a lymph gland, and may vary in size from a pea to a hen's egg. It may become calcified or cystic. The origin of the larger bodies may be a matter of considerable doubt.

FOREIGN BODIES

The two chief varieties of foreign body met with in the intestine are gall stones and enteroliths.

A *gall stone* may grow in the gall bladder to such a size that it is unable to pass along the cystic duct. In rare cases inflammatory adhesions may form between the gall bladder and the second part of the duodenum, and the stone may ulcerate through into the bowel. There it may be gripped by the circular muscular fibers, and give rise to one variety of acute obstruction.

It might be supposed on *a priori* grounds that rupture would more commonly occur into the transverse colon, and that the stone would be found in the large intestine. As a matter of fact in the great majority of cases the obstruction occurs in the small intestine. Moreover the obstruction usually occurs at the lower end of the small intestine. One might expect the stone, especially when large, to produce such intense irritation that the bowel would grip it and impede its further progress, but such is usually not the case. In one example of the condition studied in the Winnipeg General Hospital the stone was one of the largest that I have ever seen. It was a pure cholesterol calculus, almost spherical, and about the size of a pigeon's egg, and yet it apparently produced no symptoms until it reached the lower end of the ileum, where it became impacted, caused acute obstruction, and was then successfully removed.

An *enterolith* consists of a mass of calcium and magnesium phosphate which forms in the bowel, or more commonly in some pocket or diverticulum. It acts as a local irritant, and may produce obstruction, usually chronic but in some cases acute.

Tumors Other than Carcinoma.—Sarcoma of the bowel is quite rare, unless lymphosarcoma be included in this group. It is commoner in the small than in the large intestine. It is more massive than carcinoma (Fig. 184), but is less likely to produce obstruction, as it does not arise from the mucous membrane. The most common type is leiomyosarcoma, but fibrosarcomas also occur.

Lymphosarcoma may commence in the lymphoid tissue of the bowel. The wall of the bowel is diffusely infiltrated and thickened, so as to resemble a garden hose. The abdominal lymph nodes are also involved.

Adenoma, *fibroma*, *lipoma* and *myoma* when they occur in the small intestine are usually pedunculated. Such a tumor may form the starting point of an intussusception.

Multiple adenomata of the large intestine are often present in great numbers. They are usually pedunculated, but may be sessile. They sometimes show a hereditary tendency, occurring in a large proportion of the members of a family in succeeding generations.

Fig. 184.—Sarcoma of the small intestine.

Fig. 185.—Polyposis of large bowel.

The chief importance in these growths is the tendency of one of them to develop into carcinoma. This is most apt to occur in the rectum. The incidence of carcinoma in a single adenomatous polyp is about 5 per cent. In multiple adenomatosis there may be as many as one or two thousand (Fig. 185), so that the chance of escaping carcinoma in

such a case is infinitesimal. The incidence of carcinoma is naturally directly proportional to the number of adenomata.

Carcinoid tumors of the intestine are of the same nature as the much commoner carcinoids of the appendix (see Chapter XV). They occur in the small intestine (Fig. 186), rarely in the colon. Though usually single, they may be multiple. They are locally invasive, and, as in exceptional cases they may metastasize, they cannot be regarded as benign tumors; at the same time their malignancy is of very low grade. The tumor, which arises from the argentaffine Kultschitzky cells in the depths of the mucosal glands, forms a small circumscribed nodule in the submucosa which projects into the lumen. The cut surface is yellowish. It is composed of rather small cuboidal cells closely packed in nests or masses. Complete identification requires the demonstration of argentaffine granules in the tumor cells by silver impregnation, but the histological structure is usually sufficiently clear without this. In the metastasizing cases there is involvement of abdominal lymph nodes and liver.

Fig. 186.—Carcinoid tumor of small bowel.

ACTINOMYCOSIS

The usual site is the cecum, but the pelvic colon may also be affected. A common starting place is the appendix, and when the patient is first seen an appendectomy has often been done some weeks before for what appears to be an attack of acute appendicitis. The appearance is that typical of an infective granuloma, namely ulceration of the mucosa and great thickening of the wall of the bowel. Suppuration occurs and the ray fungus may be found in the pus. There is marked tendency to form multiple sinuses and fistulas which open on the abdominal wall. It is but natural that the clinical diagnosis should be a matter of the greatest difficulty, and even after the abdomen has been opened mistakes will often be made. The two conditions with which it is most likely to be confused are tuberculosis and malignant disease.

Embolism of the Superior Mesenteric Artery.—This condition has already been fully discussed in Chapter VI.

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CHAPTER XV

THE VERMIFORM APPENDIX

The vermiform appendix holds rather a peculiar position in medical science. It is a small and somewhat insignificant organ, but so are other organs which are now known to be all-important to the animal economy, such organs as the pituitary, the parathyroids, and the adrenals. The appendix owes its position of eminence not, however, to its physiological importance, but to the extreme frequency with which it becomes the seat of pathological changes.

Anatomy.—The position of the appendix varies considerably. As a rule it springs from the inner and posterior aspect of the cecum about one inch from the ileo-cecal valve, and points upwards and to the left towards the spleen. It may be retrocecal in position, passing upwards behind the cecum and ascending colon. Such a position favors the localization of an appendicular abscess. Or it may hang down over the brim of the pelvis, with the danger of infecting the pelvic peritoneum and viscera in case of inflammation.

These are the principal positions of the appendix, but when the mesentery of the cecum is abnormally long and lax it may be found in almost any part of the abdomen.

Its *length* is also variable. It averages from 3 to 4 inches, but may be a mere stump, or as long as 9 or even 10 inches.

In *external appearance* the normal appendix is of a light pink color, and soft and velvety to the touch. Any hardness or rigidity is an indication of inflammation either past or present. Concretions or foreign bodies may easily be felt from the outside. The subperitoneal vessels can hardly be distinguished by the naked eye. It must be clearly remembered, however, that an appendix may appear normal to the naked eye, both in external appearance and even when cut into, and may yet be the seat of active inflammation. Lockwood, in his memoir on the appendix, cites several cases which bear this out very forcibly.

On *section* the lumen is seen to be Y-shaped, and is surrounded by the mucosa which is about 1 mm. io diameter. Separated from the mucosa by the somewhat open submucosa is the muscular coat, consisting of an inner circular and an outer longitudinal layer. The peritoneal coat can hardly be seen by the naked eye, and under it is the equally thin subserous layer.

The *mucous membrane* consists of a single layer of columnar epithelium, numerous tubular glands lined by similar cells, and masses of lymphoid tissue. The surface epithelium constitutes the most important barrier against bacterial invasion. When it is broken down the bacteria in the lumen have ready access to the wall of the appendix.

The *lymphoid tissue* is arranged partly as a fine adenoid reticulum surrounding the bases of the glands, partly as definite follicles which are

situated at the junction of the mucosa and submucosa. The follicles vary in number, but five or six may usually be counted in a transverse section through the middle of the appendix. Lockwood estimates that an appendix of ordinary length contains from 150 to 200 of these follicles. In the middle of the follicle is the "germinal center," pale in color, and containing proliferating cells which may show mitotic figures. The outer part consists of a dense mass of darker cells.

It is probable that the abundant lymphoid tissue constitutes a defense against bacterial invasion. This tissue is most abundant during adolescence, and begins to atrophy about the thirtieth and sometimes as early as the twentieth year. These facts may have some bearing on the pathology of the organ. Sometimes there is a great increase in the number of the lymph follicles. (Fig. 187.)
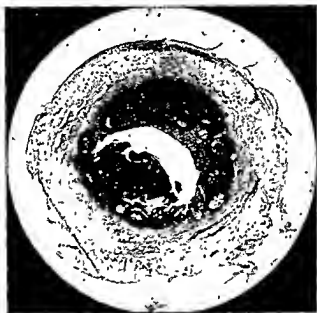
Fig. 187.—Marked lymphoid hyperplasia in the appendix. × 6.

The submucosa consists of delicate connective tissue, well supplied with blood vessels and lymphatics. It varies greatly in thickness as the result of disease. In acute inflammation it becomes swollen, edematous, and crowded with inflammatory cells. As the result of repeated attacks it becomes converted into dense fibrous tissue. It is separated from the mucosa by the muscularis mucosae, but this band is not nearly so well developed as in the rest of the intestine, and may be completely absent opposite the lymphoid follicles.

So far nothing has been said of the nervous mechanism of the appendix. There are two sympathetic nerve plexuses, Meissner's plexus in the submucosa and Auerbach's plexus in the muscularis. Associated with these, particularly the latter, are groups of ganglion cells. Reference must be made here to Masson's important contributions to the structure of the appendix. He has shown that an intimate relationship exists between

the non-medullated nerves and the plain muscle fibres of the appendix, and he describes what he calls a musculonervous complex of the submucosa. In the infant, muscle bundles can be seen to pass inwards from the circular muscle coat and outwards from the muscularis mucosae, and these anastomose in the submucosa. The nerves of Meissner's plexus accompany these bundles, and together they form a musculonervous complex. In the adult the muscularis mucosae is much less marked, being interrupted by the lymph follicles, and the invasion of the submucosa by muscle bundles is less easily detected. In pathological states, however, as will be described later, there may be great hyperplasia of the musculonervous mechanism of the submucosa. These changes are most easily detected in sections stained by Masson's trichrome methods which serve to distinguish the plain muscle from the fibrous tissue of the submucosa, but they can also be made out in ordinary sections stained with hematoxylin and eosin.

The *muscular coat* consists of on inner circular layer about one millimeter in thickness, and an outer longitudinal layer of about half that diameter. When the appendix is distended by disease the circular coat tends to become compressed, but the longitudinal fibers are separated from one another, so that the former affords a more efficient barrier than the latter.

The *lymphatics* of the appendix form a large plexus in the mucosa and submucosa. In the subserosa they run in a longitudinal direction, so that injected material extends from the apex to the base of the organ. Vessels also pass from the submucous to the subserous coats. It is therefore evident that infection may pass transversely across the appendix, but that spread along the organ will be confined mainly to the subserosa.

APPENDICITIS

In his exhaustive monograph on the subject Kelly remarks that "the vermiform appendix constitutes a microcosm, in which all the various diseases to which its component anatomical elements are liable in other parts of the body may occur." Of these by far the most frequent and important is acute inflammation.

Applying the principles already studied in the chapter on Inflammation we may say that the terminations open to inflammation of the appendix are (1) resolution with return to the normal, (2) tissue destruction with suppuration, ulceration, or gangrene, and (3) healing with the formation of cicatrices. It is seldom, however, that resolution is complete, leaving behind no ill effects. An appendix which has been the seat of a previous attack of inflammation may appear perfectly normal to the naked eye, but microscopic examination may show serious changes which strongly predispose to future inflammatory attacks.

We may therefore speak of (1) catarrhal appendicitis, (2) suppurative appendicitis, and (3) fibrosis of the appendix. The last named is often called chronic appendicitis, but chronic inflammatory changes are not actually going on. The appendix is damaged and fibrosed, and is liable to recurring attacks of inflammation which vary in severity from the very mild to the very severe.

Etiology.—It is a curious fact that although appendicitis is such a very common disease the etiological factors still remain vague and indefinite. The frequency of the disease is only of recent date. Appendicitis was present, but was relatively rare, in highly civilized communities until the end of the nineteenth century. Since that time it has become very common in these countries. The rise began in England about 1895, and was pronounced between 1895 and 1905; since then it has been fairly stationary. It was in the cities and amongst the better-off classes that the rise was most marked; inmates of institutions on a plain diet are relatively immune.

The national distribution of the disease is very interesting. It is common in highly civilized countries such as Great Britain, the United States, France, and Germany. In Denmark and Sweden it is lower. In Spain, Greece, Italy and the rural parts of Roumania it is very low. Lucas-Championnière found one case of appendicitis in 22,000 patients among Roumanian peasants, whilst in the cities of Roumania he found one case in every 22 patients. McCarrison states that during the 9 years that he practiced among the hill tribes of North-West India he never saw a case of appendicitis. In Asiatics, Africans, and Polynesians it is very rare, unless they take to European food; then it becomes common. In wild animals it is rare or unknown. In animals in captivity it is common, especially amongst the apes in Zoological Gardens.

As regards the *exciting cause* there are two main factors, obstruction and infection. The experimental work of Wangensteen and Bowers coupled with observations on human cases goes to show that obstruction plays an all-important part, especially in gangrenous and perforating appendicitis. Wangensteen and Bowers found that in the dog complete obstruction of the infected cecal appendage was always followed by acute inflammation. Obstruction without infection (the appendix being previously washed out) or infection without obstruction did not cause inflammation. In man it would appear that pressure-distension is the exciting factor, bacterial invasion of the injured wall being a secondary event. According to this view, acute appendicitis is a form of closed loop intestinal obstruction. Obstruction may be due to a concretion, to swelling of the abundant lymphoid tissue, to contraction of a sphincter-like mechanism at the base of the appendix, to fibrous contraction of the proximal end from previous attacks, to kinking of the appendix by a band or fold, and occasionally to masses of *Oxyuris vermicularis*. An impacted fecalith is responsible in about 80 per cent of cases. I have seen acute appendicitis caused by obstruction of the proximal end of the appendix by carcinoma of the cecum. When in the course of an operation a needle is passed through the tip of the uninflamed appendix and attached to a column of water, not a drop of water will escape into the cecum until a pressure of about 40 cm. is reached. As the result of obstruction the intraluminal pressure is increased, the lumen is distended, the venous return is interfered with, vessels rupture, hemorrhage occurs, the poorly oxygenated wall is invaded by bacteria, the swelling increases still further, until finally perforation may occur. In 72 per cent of cases of acute suppurative appendicitis, Wangensteen and Bowers found obstruction, and in 100 per cent of cases of gangrenous appendicitis. It is of interest to note that

one of the earliest and best papers on obstruction as a causal agent in acute appendicitis is that of Van Zwalenburg in 1904.

Mild cases are more likely to have had multiple attacks previously, because here the obstruction is slight and is overcome spontaneously, so that the patient goes on to another attack. The severe (gangrenous) cases have a much lower incidence of previous attacks, because here the mechanism cannot be overcome except by appendiceal perforation. This agrees with the observation that fecaliths are much more common in gangrenous and perforated appendicitis. In a personal communication Bowers remarks that in a patient on the operating table under local anesthesia, the train of symptoms characterizing previous attacks can be induced by increasing the intraluminal pressure by slowly injecting saline into an appendix which has been ligated at the base.

Although the importance of obstruction has been emphasized, the possibility of hematogenous infection from the throat, tonsils, etc., is by no means excluded. Not infrequently an acute attack is preceded by a sore or septic throat.

Wilkie has drawn a distinction between acute appendicitis and acute appendicular obstruction. It is true that two classes of cases can be distinguished clinically, one in which the symptoms are fulminating and local rather than general, the other in which the onset is more gradual and in which constitutional disturbance is more pronounced. The former group has been designated acute appendicular obstruction, but it simply means the more pronounced the obstruction, the more fulminating and local in type will be the clinical picture. It is in these acute cases that trauma to the abdominal wall may sometimes act as a causal agent, which may be a point of importance in certain Workmen's Compensation cases.

Reference has already been made to the prevalence of acute appendicitis in civilized communities and in cities as compared with uncivilized communities and rural districts. Speaking generally it may be said that in the former proteins are consumed, in the latter carbohydrates. Post-mortem statistics suggest that fibrosis and scarring due to mild attacks of inflammation are common in all nations, but the urgent gangrenous type is confined to the meat-eating peoples. Acute appendicular disease is more than twice as common in the male as in the female. This may be *due to the fact that the young adult male is more subject to strain and trauma*, and that his diet is usually richer in protein than that of the female. Finally, the acute form is rare in the first years of life and in old age. In the former obstruction can not readily occur, whilst in the latter the lumen is often obliterated by fibrotic changes.

Appendicitis may occur at any age, but it is rare in infancy and old age. It is commonest during the second and third decades. I have performed an autopsy, however, on a child two years of age with a gangrenous appendix, the clinical diagnosis being lobar pneumonia.

Acute Catarrhal Appendicitis.—Although this condition is frequently diagnosed clinically, it is by no means commonly found by the pathologist. In true catarrh the inflammation is confined to the mucous membrane, but in the appendix the natural tendency is for the infection to extend to the deeper structures, and to set up a diffuse inflammation.

The appendix is slightly swollen, and the subperitoneal vessels are

dilated and tortuous. There is, however, no loss of the normal peritoneal sheen. The mucous membrane is swollen, edematous, and congested, and the surface is frequently covered with mucus.

Microscopically the surface epithelium is intact but there is proliferation of the epithelial cells lining the glands. The stroma is congested and edematous, and contains considerable numbers of leucocytes. The germinal centers of the lymph follicles are unduly prominent, and contain many proliferating cells. The remaining coats of the appendix are normal.

Resolution may be complete, but residual changes are often left which predispose the appendix to subsequent diffuse attacks of a more serious character.

Acute Suppurative Appendicitis.—The infection usually commences at the bottom of one of the crypts, and extends from the mucosa throughout the submucous coat.

Fig. 188.—Acute appendicitis with peritoneal exudate.

The appearance of the appendix is very different from that seen in the catarrhal stage. The whole organ is enlarged, being elongated and thickened, it may be to several times the normal diameter. The color is bright or dark red, and there may be a purulent exudate on the peritoneal surface (Fig. 188). Under the peritoneum there may be extravasations of blood, and perhaps yellowish spots indicating the formation of an abscess. The tip is often club-shaped, and the distension of that part may be marked. The mucosa is swollen and extremely congested. It is usually granular, and may be covered with warty processes. Erosions or ulcers of the mucosa are common. The ulcers are of varying depth, usually involving the mucous and submucous coats, but in some cases passing through the muscular coat as far as the peritoneum, where they may perforate. The lumen is filled with mucopurulent material. If, as so commonly happens, there is obstruction owing to an impacted fecolith, dilatation of the lumen and thinning of the wall are salient features. The contents are liquid and under pressure. The transition from normal to abnormal may be very abrupt.

Microscopically all the coats are congested, edematous, and infiltrated with inflammatory cells (Fig. 189). These changes are most marked in the submucous and subserous coats. The epithelium of the surface and that lining the glands shows degenerative changes which may only be slight, but in many cases are profound. The glands are compressed owing to swelling of the interstitial tissue. Whole sections of the mucosa may be necrosed and cast off into the lumen, these ulcers occurring especially at the points where the lymph follicles approach the surface. The surface

of the ulcer is covered with fibrin and desquamated cells. If the process has gone on to suppuration small abscesses may be present in the wall. Threads of fibrin are frequently present, not merely on the peritoneal surface, but also in the inflammatory exudate in the substance of the wall. Hemorrhages may be scattered throughout the inner coat, often leaving permanent collections of pigment. The vessels are often thrombosed, a condition which may result, although fortunately only in exceptional cases, in the formation of septic emboli and pyemic abscesses in the liver.

In striking contrast to what we find in so-called chronic appendicitis in acute appendicitis the symptoms are readily explained by the loca

Fig. 189.—Acute suppurative appendicitis with peritonitis. All the coats are involved

changes. The hyperemia, edema, and cellular exudate produce distension of the wall of the appendix with stretching of the sympathetic plexus which lies in the outer part of the wall. The stimuli pass to the semilunar ganglia and give rise to nausea, vomiting, and general abdominal pain. In the course of a few hours the inflammation has reached the serous coat, and the resulting inflammation of the *parietal* peritoneum is responsible for the local pain and muscular rigidity. In severe cases the generalized abdominal pain disappears after 24 hours; this is because the sympathetic nerve endings have been destroyed by the inflammatory process. For the same reason the most severe and fulminating cases, in which gangrene of the appendix rapidly develops, may be associated with comparatively trivial local symptoms.

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of acute inflammation, and must not be taken as an indication of chronic inflammation.

Chronic Appendicitis.—The clinical and pathological problems of acute appendicitis are simple compared with those of chronic appendicitis, the condition to which the clinician applies the name of the chronic appendix. The diagnosis of chronic appendicitis has become one of exceeding frequency, and it is one which it is often as difficult to refute as to confirm. Even when the appendix is in the hands of the pathologist he may find it difficult to say whether or not the specimen should be considered one of chronic inflammation.

The *symptoms* attributed to chronic inflammation of the appendix are legion, but the classical symptoms of the condition are vague abdominal pains, slight tenderness over McBurney's point, constipation as a rule, flatulence, "bilious attacks," "bilious headaches." The condition so aptly named by Moynihan appendix dyspepsia is characterized by pain coming on from half an hour to an hour after eating; there is no fixed interval of relief after a meal as in gastric ulcer, and the pain is described as coming on "at any time" after a meal; it is worse on exertion and after exercise. Hertzler, in a very penetrating study of chronic appendicitis written from the viewpoint of a pathologist as well as a surgeon, gives the clinical picture presented by one writer as nervousness, headache, melancholia, irritability, insomnia, dizziness, general weakness, poor appetite, inability to think clearly, and habitual constipation. "I become afflicted," remarks Hertzler, "with all these symptoms whenever I contemplate the picture of chronic appendicitis."

Nothing is more difficult than to prove that the symptoms in all of these cases are due to lesions in the appendix. The pathological report depends largely on the personal views of the pathologist, and it has been said that to-day every appendix is condemned by some pathologist somewhere. Hospital statistics may also be quite misleading. The fact that the patient leaves the hospital with a diagnosis of "cured" means nothing. Visceroptosis is common in girls from 12 to 24 years of age, and these patients often have tenderness on pressure in the right iliac region. Removal of the appendix affords relief for a few weeks, largely because the patient is kept in bed, but when she returns home the discomfort soon returns, and the operation is as unsatisfactory to the surgeon as to the patient.

Fig. 190.—*Gangrenous appendicitis. The distal third is gangrenous, and is about to perforate at the lower border.*

The course of the disease depends largely on the peritoneal changes. Although some degree of peritonitis is always present, localizing adhesions may prevent the spread of the inflammation, even when a local abscess has formed. On the other hand, and more especially in cases of streptococcal infection, the inflammation may extend rapidly from the submucous to the peritoneal coat, and set up a general spreading peritonitis even when the appendix does not appear to be very acutely inflamed. In these cases the symptoms of peritonitis mask those of the local appendicular lesion.

Gangrenous appendicitis is merely a further stage of the acute diffuse variety. There is death and putrefaction of the tissues of the appendix, either local or general, due in every case to interference with the blood supply. Such interference may be due to thrombosis of the vessels, to vascular obstruction from kinking or stricture of the appendix which is made acute by the sudden inflammatory swelling, or to pressure on the inflamed and swollen mucosa by a concretion.

If the main artery to the appendix be affected, or if there is obstruction and strangulation of the proximal end of the appendix, the whole organ may become gangrenous. More common is the development of a localized patch of gangrene, often at the tip (Fig. 190), but there may be two or three such patches in both the proximal and distal parts. The affected area, which is of a green and later an almost black color, often corresponds to the position in the lumen of a hard concretion, which by pressure on the inflamed wall undoubtedly contributes to the production of the gangrene.

In cases of severe inflammation the meso-appendix shares in the general changes. It becomes thickened, edematous, congested, and infiltrated with inflammatory cells. Patches of the mesentery fat may be of so dark red a color as to resemble the appendix itself.

Perforation may occur at any stage of acute appendicitis. It may take place within the first 36 hours, or only late in the disease. It is due to necrosis of the coats of the appendix, of which the chief cause is the pressure of a concretion. Or it may be due to gradual erosion of the various layers. In rare cases it is due to the presence of a sharp foreign body such as a pin. The perforation may be pinpoint in size, or may be a large yawning opening with ragged edges. It is commonest at the tip, but may occur at any part. A small and unsuspected perforation may be found to be sealed over with a tag of omentum.

Retrogression.—As the patient recovers, the acute process in the appendix subsides. The tissue which has been destroyed will be replaced by fibrous tissue. In this way the entire mucosa may become converted into a fibrous mass with obliteration of the lumen. The submucosa and to a lesser extent the muscularis may also be fibrosed. A person may, however, pass through a typical attack of acute appendicitis, and when the appendix is removed some time later no evidence of the former attack can be detected. In such a case there can have been no destruction of tissue. In addition to the fibrosis, vascular dilatation and collections of inflammatory cells may be observed for a period varying from a few weeks to two or three months. These merely represent the aftermath

of acute inflammation, and must not be taken as an indication of chronic inflammation.

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The problem is evidently a very difficult one and it is as important as it is difficult. The great majority of surgeons are firmly convinced of the existence of chronic appendicitis as an entity. They therefore remove the appendix when the patient complains of some of the above-mentioned symptoms. The pathologist is frequently consulted as to whether a given appendix which has been removed could produce the symptoms complained of, which is tantamount to asking his opinion about chronic appendicitis. It appears to the writer that no pathologist is in a position to return a satisfactory answer to this question. The man to settle the matter is a surgeon with a good pathological training who will follow the subsequent history of his private cases for a number of years. This is the experimental method, and if the experiment is properly performed it should answer the question as to the significance, from the point of view of the production of symptoms, of certain gross and microscopic deviations from the normal appendix. One of the best studies of this kind is that of Hertzler, on some 2000 patients in his own practice with pain and tenderness in the region of the appendix. He arrives at the conclusion, with which the writer is in agreement, that the fibrotic and other changes supposed to be indicative of chronic appendicitis are wholly inadequate to explain the symptoms ascribed to them.

Morbid Anatomy.—Inflammation, whether acute or chronic, is the local reaction to an irritant. It is therefore a process, not a state. This is the rock on which the "chronic appendix" school has foundered. The features which induce the surgeon to remove the appendix when the abdomen is opened are the result of fibrosis. But the fibrosis is itself the *result* of a previous inflammation, not an indication of an existing inflammatory process. It is a fibrosed, not an inflamed appendix.

At first sight, then, it might appear that fibrosis, particularly of the submucous coat, is a sure indication of previous inflammation. When the appendix is buried in adhesions and shows marked kinking it is safe to say that the condition has been inflammatory; this is the picture seen in relapsing appendicitis, where there is a succession of definite acute attacks. Often, however, the appendix is quite free from adhesions, but shows the condition known as appendicitis obliterans, in which fibrosis of the wall leads to obliteration of the lumen, an obliteration which commences at the tip and gradually progresses toward the base. Such an appendix is commonly regarded as pathological, but it is difficult to see how it can be productive of symptoms unless there is at the same time a stricture at the proximal end.

On this matter there is much difference of opinion. Aschoff is very positive that obliteration from fibrosis is always due to a previous inflammation, whereas Ribbert, Zuckerkandl, and other authorities regard it as a more or less natural atrophic retrogressive process associated with the advance in years. In a series of 400 autopsies Ribbert found that 25 per cent of the appendices showed partial or complete occlusion of the lumen. The process of obliteration may commence at any point, but it generally begins at the tip and proceeds toward the base. Out of 300 specimens removed in the gynecological department of the Johns Hopkins Hospital, Kelly found that 45 presented some degree of obliteration. In a large series of appendices studied by me in the Winnipeg General

Hospital many which were removed "en passant" in the course of another operation showed marked obliterative fibrosis unaccompanied by any symptoms. If the fibrosis is associated with stricture of the proximal end, symptoms due to appendicular obstruction may perhaps be expected, but when there is no stricture it is not easy to see why fibrosis in itself should give rise to symptoms unless, by interfering with the contraction of the muscular tube, it should prevent the normal emptying of the appendix. When, therefore, a fibrosed appendix is found in a case of chronic digestive disturbance it is hardly justifiable to assert with confidence that the condition has been merely one of "chronic appendix." The after history may tell a very different tale.

Sir Arthur Keith regards the appendix as one of those structures which, like the hair of the scalp, is liable in some persons to undergo an abiotrophy, a premature atrophy or senility. "If we could follow the life-histories of 1000 modern Europeans from birth to their seventieth year the following would be the fate of their appendices. By the end of the tenth year the lumen of this structure would be partially or completely obliterated in 40 of them; by the twentieth year the same fate would have overtaken 70 more; by the thirtieth year 60 others would have been added to the list; by the fortieth year 80 further cases of obliteration would have occurred; by the sixtieth year there would be 110 additional cases. Of the 1000 people who reached the age of 70, only 500 of them would retain their appendix in an unblemished functional state; in the other 500 the appendix would have undergone a premature atrophy at succeeding stages in the journey through life." In this the appendix keeps company with all structures which are of a lymphoid nature.

The most characteristic feature is the thickening and rigidity of the organ. When the normal appendix is rolled between the fingers the walls are soft and the tube collapsible. The fibrosed appendix feels like a rigid incompressible tube. It may be longer than normal, but more often is shortened. It may be as thick as the little finger. The peritoneal vessels are dilated and as tortuous as a corkscrew, and the color is redder than normal. Pale patches, particularly at the tip, indicate an obliterative process. There may or may not be adhesions: when present they are always an indication of previous inflammation. The mesoappendix is often thickened and shortened, as the result of which there may be kinking of the appendix.

On section the normal stellate appearance of the lumen is lost, and it remains circular and patulous. The lumen may be dilated owing to atrophy of the mucosa, or narrowed from the general thickening of the walls. Often the proximal part may be contracted, the distal part dilated. If the stenosis of the proximal part is complete, the remainder of the appendix may be distended with clear serous fluid (hydro-appendix or cystic appendix) or with pus (pyo-appendix or empyema of the appendix). The mucosa is usually thickened, but may be so thinned that it can hardly be seen. The normal smooth glistening appearance is lost, and the mucosa may be markedly granular, or smooth and glazed. It may be much congested, and minute petechial hemorrhages may be scattered over the surface. These are usually more marked in the distal part. In many of our cases we have been surprised to find these petechial

hemorrhages present in appendices which were removed incidentally from patients who presented no symptoms of appendicular disease. The occurrence of pigment granules is referred to in the microscopic description. The chief thickening is in the submucosa, which may constitute the greater part of the wall.

In appendicitis obliterans the gross picture is different. The withered appendix, which is very firm, is atrophic and shrunken, it may be, to the dimensions of a piece of stout string. The color is* pale, uniformly so when the obliteration is complete, patchy when the process is partial. On section the appendix is seen to consist of two layers, an outer muscular layer, and an inner fibrous mass which includes what was once mucosa,
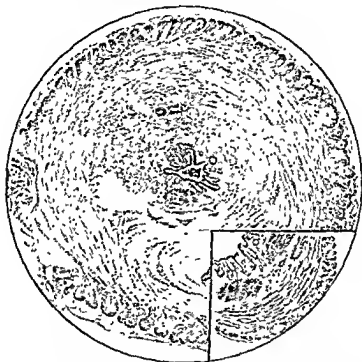
Fig. 191.—Fibrosis of appendix; inset shows normal thickness of the coats.

submucosa, and lumen. The lumen may be completely obliterated, or it may be represented by a mere chink.

The *microscopic picture* varies considerably, but fibrosis is the dominant feature (Fig. 191). This is most marked in the submucosa, which may be converted into a thick fibrous ring. It often contains collections of lymphocytes. The subserous coat is also fibrosed, and may show lymphoid collections of cells, usually perivascular in distribution. The lymphatics in this coat may be distended with lymphocytes. The muscular coat is usually atrophied, but the circular fibers sometimes show hypertrophy. The condition of the mucous membrane varies. Sometimes it shows little change, in other cases its stroma is infiltrated with lymphocytes and plasma cells, and in still others it is completely replaced by

fibrous tissue. An occasional feature is the presence of very large numbers of eosinophils both in the mucosa and submucosa. These are most often seen after an acute attack, but in many of my own cases there has been no history of such an attack. The fibrosed submucosa may contain a very large amount of fat, so much so that it can be recognized on the cut surface with the naked eye from its light yellow color.

Reference has already been made to Masson's conception of the musculonervous complex of the appendicular submucosa. He points out that many adult appendices with a history of former acute attacks or with the syndrome of chronic appendicitis show three characteristic features: (1) narrowing of the lumen, (2) great diminution or absence of the lymph follicles, and (3) thickening of the submucosa. Such appendices also show changes in the muscle and nerves of the submucosa, changes in the nerve plexus of the mucosa, and hypertrophy of the muscle coat and of Auerbach's plexus.

The *submucosa* shows a remarkable hypertrophy of the musculonervous complex. The muscle fibers passing in from the muscular coat and out from the muscularis mucosae are thick, and are penetrated by the hyperplastic nerves of Meissner's plexus. The interstices between the bundles are occupied by a delicate nervous plexus with many ganglion cells. Most of the thickening of the submucosa in cases of lymphoid atrophy may be due to this musculonervous hyperplasia. The amount of nervous tissue in such an appendix is remarkable. The *mucosa* may be thickened owing to hyperplasia of non-medullated nerves, and may contain great numbers of small circumscribed neuromas, sometimes as many as 40 in each cross section. The *muscularis* occasionally shows hypertrophy of the circular coat, associated with marked

Fig. 192.—Carcinoid tumor of appendix showing the characteristic yellow ring.

hyperplasia of Auerbach's plexus, together with the presence of numerous ganglia, the cells of which may be two or three times larger than normal. It appears as if the change commences in the submucosa, and spreads later to the mucosa and muscularis. The excessive growth is probably the result of previous inflammation, regeneration of nerves following the process of destruction.

It is not possible to say at present what is the exact clinical significance of these histological observations of Masson's. It is not claimed that every thickened appendix is to be explained on these grounds. But it is certainly possible that in some cases of "chronic appendicitis" the symptoms may be related to these remarkable changes in the sympathetic nerve supply to the appendix. The work of Simard in Masson's laboratory suggests that there may really be such an entity as "neuro-

genic appendicitis." Further work on the correlation between these pathological findings and the clinical course is much needed.

Foreign Bodies.—In the diseased appendix it is common to find foreign bodies, which may simulate all kinds of familiar objects such as grape seeds, cherry stones, etc. It used to be commonly supposed that the stones of various fruits found frequent lodgment in the appendix, where they acted as the exciting cause of attacks of acute inflammation. It is now known that these are of the rarest occurrence, although it is true that many curious objects may find their way into the appendix. Pins, bristles, the stones of fruit, grains of corn, even small shot have been found in the appendix, but in many such cases the appendix may be quite normal.

Fecal concretions, however, are of very common occurrence. They vary greatly in consistence, being in some cases soft and putty-like, in others as hard as stone. Quite often they present a curiously laminated appearance which may cause them to be mistaken for gall stones. It is these concretions which were formerly mistaken for the stones of fruit.

The formation of a concretion is favored by stenosis of the proximal end of the tube, leading to a condition of stagnation within. The prominent part which an impacted concretion may play in the production of an acute attack of appendicitis has already been emphasized.

Carcinoid Tumors.—One of the most interesting lesions of the appendix is that which is described in the literature as primary carcinoma of the appendix. It is interesting because the histological picture suggests carcinoma, whilst the clinical course is that of a benign lesion. At the same time it must be remembered that a true adenocarcinoma may occur in the appendix as in any other part of the bowel, but it is extremely rare. As a rule carcinoid tumors behave in a benign manner, although they often infiltrate the wall of the appendix. Occasionally, however, they may metastasize to regional lymph nodes and also to the liver.

The condition is met with in the routine examination of appendices, being present in about 0.3 or 0.4 per cent of appendices removed surgically. It is rarely if ever seen in an otherwise normal appendix. The appendix is thickened and fibrosed, apparently as the result of previous inflammation, but the lesion itself does not appear to give rise to any characteristic symptoms. Wilkie has described a number of cases in which the tumor was situated at the proximal end of the appendix, and was, apparently responsible for obstruction and acute inflammation.

The gross appearance is very characteristic, so that usually the diagnosis can be made from it alone. In 90 per cent of the cases the lesion is situated near the tip of the appendix. This is probably related to the frequency with which fibrosis commences in that region. Before the appendix is opened it appears as a small firm nodule. Cross-section reveals a yellow ring which encircles the appendix and appears to be situated in the submucous coat (Fig. 192).

Microscopically the tumor consists of spheroidal cells arranged in very definite groups or masses suggestive of a carcinoma (Fig. 193), but never showing a true gland-like arrangement, although sometimes, it is true, the cells may be grouped around a rather atypical and irregular lumen. Although usually confined to the mucous and submucous coats the cells may penetrate the muscularis, and I have seen them reach as

far as the subserous coat. The cytoplasm may be granular or may be finely vacuolated. These vacuolated cells stain red with Scharlach R and it is evident that they contain a lipoid material similar to that of the cells of the adrenal cortex and xanthoma cells. It is to this lipoid that the yellow color of the tumor is due.

The nature of the tumor has caused much difference of opinion. It should be remarked here that the tumors are not confined to the appendix, for carcinoids may be found in any part of the gastro-intestinal tract, although most frequently in the small intestine. In the appendix the tumor is single, but in the intestine it is often multiple. At various times it has been regarded as a true carcinoma derived from the epithelium of the mucosa, a basal-cell tumor analogous to the basal-cell cancers of the skin, and a tumor growing from rests of pancreatic tissue containing islets of Langerhans. An excellent discussion of the various theories will be found in a paper by Forbus. The most important contribution to

Fig. 193.—Carcinoid tumor of bowel. The growth is confined to mucosa and submucosa. × 10

the subject is that of Pierre Masson. By employing silver impregnation methods he demonstrated first that many of the cells of the tumor contained granules which were stained intensely by the silver, and second that the Kulchitzky cells of the intestine were stained in a similar manner. These latter cells are found in the gastric and intestinal mucous membrane, being scattered among the cylindrical cells of the intestinal epithelium, from 5 to 10 to each gland of Lieberkühn. These cells belong to the chromaffin system and as it appears certain from Masson's work that the carcinoids both of the appendix and the intestine arise from these cells, it is evident that the tumors should be regarded as chromaffinomas, or tumors of the endocrine system. On account of their reaction with silver salts they are also known as argentaffin tumors.

In his last communication (1928) Masson has brought forward evidence suggesting that an important relationship exists between the carcinoids and the argentaffin-cell neuromas which he had previously described as occurring in obliterated appendices. These neuromas arise

from the periglandular nerve plexus in the mucous membrane, and Masson has demonstrated the presence of argentaffin cells actually inside the nerve fibers. He has also shown that these cells appear to spring from the epithelium that lines the bottom of the glands of Lieberkühn by a process of budding; they then migrate into the nerves where they become argentaffin. This remarkable migration appears to occur as the result of an inflammatory process not sufficiently severe to cause extensive destruction of the appendix. The nerves containing these cells then grow and form neuromata. Carcinoids result from the autonomous proliferation of isolated argentaffin cells in the neuroma. It remains to be seen if this work of Masson's will be confirmed; it has at least opened up very interesting possibilities.

Tuberculosis.—Tuberculosis of the appendix is usually secondary to tuberculosis of the cecum or of the Fallopian tube. In rare cases the disease is primary in the appendix. It may commence in the mucosa or submucosa, and gradually spread till the entire appen-

Fig. 194.—Mucocele of the appendix.

dix is destroyed, and a large pericecal abscess forms which may discharge into the bowel or onto the skin surface. In other cases the first lesions are seen in the mesentery of the appendix.

Actinomycosis.—This is usually secondary to disease of the cecum, but cases have been reported where the primary focus has been in the appendix.

In *typhoid fever* the lymphoid tissue of the appendix may show the infiltration with endothelial cells which is such a characteristic change in the ileum.

Mucocele of the Appendix.—As a result of obstruction of the proximal end of the appendix it occasionally happens that the appendix becomes dilated into a cyst (Fig. 194). In a few cases complete or even partial obliteration of the lumen has not been present. These are cases in which the contents are very thick and tenacious and the muscular coat may be deficient or completely absent. The cyst is usually small, but in rare cases it may attain an enormous size. One such cyst is described as being the size and shape of a very large banana (J. H. Kelly), and one is actually said to have been as large as a man's head (Neumann).

The contents of the cyst are usually somewhat thick and mucoid, and in typhoid drops, in which the contents are watery, is a rare condition. The contents may give a reaction for mucin or pseudomucin.

These rare cysts of the appendix are of interest to the surgeon because they may be the starting point of a condition of *pseudomyxoma peritonei*, similar to that which occasionally complicates pseudomucinous cystadenomas of the ovary. As the result of rupture of the cyst the contents become implanted on the surface of the peritoneum, where they cause a proliferation with the formation of large masses like frog's spawn. The condition is probably due to implantation of the epithelial cells on the peritoneal surface, where they continue to produce their mucinous secretion, but other explanations have been suggested which are considered on page 370. The prognosis is unfavorable, but removal of the appendix may check the disease.

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THE RECTUM

The rectum is usually given separate consideration in text-books of surgery. Although it is not our intention to give a full account of the surgical conditions affecting the rectum, which will be found in any of the text-books referred to, a few of the pathological problems may be considered in this place.

ULCERS AND FISTULAE

Many of the minor, although painful and sometimes disabling lesions of the rectum occur in the region of the anal canal, and the majority of the common infective lesions of this canal originate in infected crypts of Morgagni. The *mucocutaneous junction* is the most important landmark

Fig. 195.—Sinus of Morgagni. × 35.

in this region. Below this line there is the extremely sensitive squamous epithelium of the anal canal, whilst above the line there is the insensitive mucosa of the rectum proper covered by columnar epithelium. This mucosa is thrown into longitudinal folds by contraction of the external sphincter, these folds being known as the *columns of Morgagni*. Between the lower ends of the columns there are from seven to nine shallow mucosal pockets, which extend below the line of the mucocutaneous junction for a distance of from one-quarter to one-half an inch and are surrounded by lymphoid tissue. These mucosal pockets are the *crypts of Morgagni* (Fig. 195).

Cryptitis is inflammation of a crypt caused by some irritating material becoming lodged in the diverticulum-like pouch. If the resulting inflammatory exudate is able to drain into the rectum, no great harm is done, but the opening may be blocked by inflammatory edema of the mucosa and by spasm of the sphincter. In this case an abscess will be formed, which may rupture into the rectum or may track outwards and downwards to form a peri-anal or ischio-rectal abscess. A more chronic type of cryptitis may result in fibrosis of the submucous tissue in the region of the mucocutaneous line, thus impairing the elasticity of the wall and

predisposing this narrowest part of the anal canal to laceration by the passage of large fecal masses.

Anorectal Fistula.—A fistula-in-ano is a narrow infected passage situated in the region of the anus. The fistula may be complete, *i. e.*, it has an external as well as an internal opening, or it may have only an internal opening, being then known as a blind internal fistula. Secondary abscesses may develop along the primary tract, giving rise to multiple external openings and offshoots from the original fistula. The great cause of anorectal fistula is infection in the region of the mucocutaneous junction, commonly an infected crypt of Morgagni.

The internal opening at the mucocutaneous line may be marked by a shallow ulcer or there may be an indurated nodule of granulation tissue. The fistulous tract itself may feel like an indurated cord owing to inflammatory fibrosis. The external opening will be marked by an area of induration, and a small amount of pus may be expressed. Should the opening be large and irregular in shape with undermined edges surrounded by purplish skin, the fistula is probably tuberculous in nature. In the great majority of fistulae the tract lies superficial to the main body of the sphincter muscle. This represents the usual plane of extension from the mucocutaneous line to the ischio-rectal fossa.

Fissure-in-ano.—Fissure-in-ano is the term given to an anal ulcer, acute or chronic, simple or tuberculous in character, situated in the anal canal just below the mucocutaneous junction. The etiological factors are: (1) trauma by the passage of a large hard stool, and (2) loss of elasticity due to chronic infection and fibrosis. At least 95 per cent of these lesions are situated in the posterior commissure, because the fibers of the external sphincter which encircle the anus fuse much more completely in front than behind, so that the mucosa of the posterior aspect of the anal canal is less strongly supported and more easily torn.

The *acute ulcer* is often a mere crack in the epithelial surface, but may nevertheless cause much pain and spasm. Healing often occurs promptly under palliative treatment. The *chronic ulcer* has thickened edges, the skin at the lower end of the fissure is often edematous, hypertrophied and undermined producing the so-called "sentinel tag," a hypertrophied papilla will usually be found at the upper end, whilst in the base of the ulcer one can sometimes see the fibers of the external sphincter crossing transversely. A *tuberculous ulcer* is characterized by a greater degree of undermining of the skin. The base presents a slough, and the edges are red, ragged and indurated. The lesion usually begins as an ordinary fissure-in-ano, which becomes infected by tubercle bacilli and in time develops into a typical tuberculous ulcer. The great majority (probably 95 per cent) of anal fissures and fistulae are non-tuberculous. The pathologist may find a pseudotuberculous reaction characterized by epithelioid and giant cells, but giant cells are not synonymous with tuberculosis and may be due merely to the irritation of foreign material. The absence of caseation is the most useful differentiating feature in the microscopic picture.

Tuberculous Proctitis.—Tuberculosis of the rectum usually takes the form of extensive ulceration. Numerous tubercles are formed in the submucosa. These coalesce, large areas of caseation are formed, and the over-

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lying mucosa becomes necrosed and cast off. The ulcers present the ragged, undercut edges characteristic of tuberculosis. So extensive may be the ulceration that the entire rectum may be involved. Tubercle bacilli are present in abundance in the discharge. Tuberculous ulceration is usually included in the list of conditions which may result in cicatricial stricture, but it is very doubtful if the lesions ever recover sufficiently for healing to occur.

Syphilitic Proctitis.—Syphilis of the rectum, particularly syphilitic stricture, was until recently thought to be of common occurrence. Any non-malignant stricture of the rectum occurring in a syphilitic person was presumed to be specific in nature. The truth seems to be that rectal syphilis is a rare disease, and that the great majority of rectal strictures are due to such venereal diseases as lymphogranuloma venereum or gonorrhea, to ulcerative colitis or amebic dysentery, or to trauma, operative interference, etc. Undoubtedly gummatous formation may occur in the rectum and may give rise to the formation of a stricture, but it is very difficult to be certain of the diagnosis, nor is the microscopic examination of much assistance.

Gonorrheal Proctitis.—This rare condition is commoner in females than in males. It is nearly always secondary to genital gonorrhea. The rectal mucosa is red and edematous, and from it there is a discharge of yellow pus. There is a tendency for ulceration to develop, with subsequent fibrosis and the formation of rectal strictures. The gonococcus is difficult to find.

Lymphogranuloma Venereum (Lymphogranuloma Inguinale).—The fourth venereal disease often involves the rectum and anal region in its later manifestations. It is caused by a virus which can be grown in tissue cultures and on the chorio-allantoic membrane of the chick. It is readily transmitted by intracerebral inoculation into monkeys, ferrets and mice. The initial lesion is on the genitalia, but it may be so slight as to pass unnoticed. In men the inguinal lymph nodes are enlarged and suppurate, with involvement and breaking down of the skin and the formation of very chronic fistulous tracts. In women the course is quite different. As the lymph from the vagina drains to the perirectal lymph nodes, the wall of the rectum is commonly involved, and an inflammatory stricture develops, usually from 3 to 5 cm. above the mucocutaneous line. This is the usual chain of events. It must be realized, however, that the usual may be reversed, so that rectal stricture may occur in the male and inguinal suppuration in the female. The Frei intradermal test with material containing the specific virus showed for the first time that lymphogranuloma inguinale, many cases of benign stricture of the rectum in women, and esthiomene (hypertrophic or ulcerative elephantiasis of the labia) are three manifestations of a single disease. Subsequently the virus was isolated from each type of lesion. In the rectal lesions and in esthiomene the microscopic picture is non-specific, but in the active inguinal lesions one sees irregular star-shaped abscesses bordered by a zone of epithelioid cells with an occasional giant cell; plasma cells are present in great numbers in the surrounding tissue.

Dysentery.—There are two forms of proctitis which may be grouped under the heading of dysentery; these are amebic dysentery and chronic

ulcerative colitis. The latter may be a chronic form of bacillary dysentery, although this has by no means been proved.

In *amebic dysentery* involving the rectum proctoscopic examination reveals ulcers of varying size, with irregular and shaggy edges, red and somewhat raised above the level of the rest of the mucosa. The edges are undermined by the amebae. The ulcer seldom extends beyond the muscle coat, but sometimes perforation may occur. Except in very severe cases the mucosa between the ulcers is normal. If the infection has not been treated there may be fibrosis with the development of strictures.

In *chronic ulcerative colitis* proctoscopic examination shows a picture which varies with the stage of the disease. The picture has already been described on page 272.

ABSCESSES

Abscess of the rectum and its neighborhood develops much more frequently in men than in women, and usually over the age of thirty. These abscesses may be divided according to their position into: (1) subcutaneous, (2) submucous, (3) ischio-rectal, and (4) pelvi-rectal.

Subcutaneous Abscess.—This originates as an infected sebaceous follicle or external hemorrhoid at the margin of the anus. The abscess usually discharges on the skin, but if it be not opened early it may burrow towards the rectum with the formation of a fistula.

Submucous Abscess.—When as a result of a tear in the mucosa infection gains an entrance, a submucous abscess will be formed. This may discharge on the mucous surface, or may burrow downwards to the skin, forming a blind fistula.

Ischio-rectal Abscess.—This begins as an abrasion or ulcer at the mucocutaneous line. The loose subcutaneous tissues become infected, and the infection then extends into the fatty spaces of the ischio-rectal fossa. An ischio-rectal abscess then develops. This is situated below the levator ani muscle. If the abscess forms near the anal canal it is called a *perianal abscess*. Occasionally the abscess may extend round the posterior edges of the levatores ani and reach the ischio-rectal abscess on the other side, forming a "horse-shoe" abscess.

Pelvi-rectal Abscess.—In a pelvirectal abscess the pus is situated *above* the levator ani muscle. Unlike the other abscesses in the neighborhood of the rectum the infection does not originate in the rectum but in some of the surrounding viscera such as the prostate, the neck of the bladder, or the pelvic bones. Not infrequently the pus makes its way through the levator ani and enters the ischio-rectal fossa.

HEMORRHOIDS

Hemorrhoids or piles is a condition in which the hemorrhoidal veins become varicose and hypertrophied. It is convenient to distinguish between two varieties: *internal piles*, involving the branches of the superior hemorrhoidal veins and covered by mucous membrane, and *external piles*, involving the inferior hemorrhoidal veins and covered by skin. The former vein opens into the portal, the latter into the systemic circulation; their radicles anastomose. If the varicosities are above the

mucocutaneous line the hemorrhoids are internal, if they are below that line they are external. The superior hemorrhoidal artery, a branch of the inferior mesenteric, divides into a right and a left division. The left division continues as one main artery, but the right division divides into an anterior and a posterior branch. For this reason there can be only one primary hemorrhoid on the left side, but two on the right side.

Etiology.—The etiological factors which may be responsible for piles are numerous and varied, but they all have this in common, that they induce a condition of congestion of the hemorrhoidal veins. Of the *central* causes the two important conditions are a failing heart and cirrhosis of the liver with portal congestion. Of the *local* causes we may distinguish between causes within the rectum and those outside the rectum. Examples of the former are any form of inflammation and chronic constipation. Constipation is the most important of all the causes of piles, partly because of the local injury to the mucosa produced by the hard scybalous masses, partly because of the pressure exerted, but perhaps chiefly from the tenesmus and straining which inevitably result in congestion and dilatation of the poorly supported hemorrhoidal veins. An important local cause for the appearance of piles, one which should never be out of mind, is carcinoma of the rectum. Amongst causes outside the rectum may be mentioned pressure from the uterus (retroversion or pregnancy), from the bladder (distension), and from the prostate (enlargement).

In addition to the direct or exciting cause of hemorrhoids it is often possible to trace a marked hereditary history in the cases. It has been suggested that as in varicose veins of the leg and in varicocele there appears to be some congenital weakness in the valves of the veins, so some such weakness should be looked for in hemorrhoids. It is much more probable, however, that it is the tendencies to constipation, etc. which are inherited.

Morbid Anatomy.—An internal pile, which may be taken as the common and characteristic variety, consists of a cluster of much dilated venules to which passes an artery, a terminal branch of the superior hemorrhoidal artery. This clump of vessels forms an elongated mass which lies in one of the columns of Morgagni, but later becomes more or less spherical. Secondary changes of considerable importance may take place. As a result of the chronic irritation a fibrosis occurs in the surrounding connective tissue which is responsible for much of the final thickening. Even more important is the occurrence of infection with the production of a periphlebitis and often phlebitis and thrombosis. The new tissue formed is therefore frequently infiltrated with chronic inflammatory cells, notably lymphocytes and plasma cells. The thrombosis may result in fibrosis with obliteration of the pile, or, if the thrombus is septic and becomes loosened, septic emboli may be set up in the liver. The patient may be subject to periodic attacks of phlebitis and periphlebitis, which are usually designated as "attacks of the piles." Such attacks tend to be self-curative, owing to the occurrence of thrombosis. Occasionally, as the result of straining on the part of the patient, the veins of an external pile will rupture, with effusion of blood into the surrounding tissue and the formation of a tense tender swelling under the skin. This may gradually

become fibrosed, so as to form a firm nodule, or the clot may become infected and converted into a subcutaneous or perianal abscess.

Miles divides internal hemorrhoids into three groups according to the stage of their development, *i. e.*, primary, intermediate, and final. *Primary hemorrhoids* are rather small, the overlying mucosa is relatively normal, and the protrusion nil except at the height of the expulsion effort during defecation. Microscopically there is no change in the mucosa, whilst in the submucosa there is slight thickening and some infiltration with lymphocytes (Fig. 196). The chief symptom is the passage of bright red blood. *Intermediate hemorrhoids* result from repeated protrusion, being elongated and thickened. Microscopically the mucosa is hyper

Fig. 196.—Hemorrhoids, showing the large blood spaces just under the columnar epithelium of the rectum and the stratified epithelium of the skin.

trophied, the submucosa edematous and infiltrated with large numbers of lymphocytes, and there is fibrous thickening of the walls of the veins. The main symptom is protrusion, but the hemorrhoid can be reduced manually; bleeding is less marked. The *final stage* is marked by constant protrusion of the hemorrhoid, which cannot be reduced. Thickening is still more marked, the submucosa is markedly fibrosed, and the partly obliterated veins are sheathed in dense fibrous tissue. The main symptoms are protrusion and soreness, there being very little bleeding.

The most important symptom of piles is hemorrhage. This, when continued over a long period of time, may lead to a profound degree of anemia the cause of which may never be guessed, for the actual blood lost at any one time may be comparatively slight. The complexion becomes clay-

colored, but the anemia is secondary in type, and should not be mistaken for the pernicious form of the disease.

INNOCENT TUMORS OF THE RECTUM

The innocent tumors of importance in the rectum are adenoma and papilloma.

Adenoma.—Perhaps the most interesting characteristic of adenoma of the rectum is its age incidence, for the majority of cases occur in childhood. The cases which occur in adult life differ from the cases of childhood in that they attain a much larger size, are usually sessile and often multiple, and not infrequently become malignant.

The adenoma of childhood is single and almost invariably pedunculated. The pedicle may grow to a great size owing to the constant traction exerted by the contraction of the bowel. In some cases it may become 4 or 5 inches long. Such a tumor is known as a rectal polypus. It is usually about the size of a raspberry, and with its dull red color and nodular surface it often resembles that fruit very closely. Hemorrhage is the principal symptom.

Microscopically the tumor consists of a wonderfully regular proliferation of the glands of the mucous membrane, the regularity forming a marked contrast to the wild disorder seen in adenocarcinoma. There is, of course, no invasion of the muscularis mucosae.

Papilloma.—This tumor, also called villous tumor of the rectum, although rare is of importance on account of its liability to become malignant. In many respects it resembles the villous papilloma of the bladder.

Fig. 197.—Papilloma of large bowel.

Occurring in adults, as a rule sessile or if pedunculated only slightly so, the mass is covered by long villous processes which wave gracefully to and fro when the specimen is placed in water. Each process is covered by one or several layers of cylindrical cells supported by a delicate stroma which is so vascular that hemorrhage occurs with great readiness (Fig. 197). The extent of these tumors is sometimes remarkable. There is a specimen in the Pathological Museum of the University of Manitoba in which an area on the rectum the size of the palm of the hand is covered by real villous processes. (Fig. 198.) The tendency towards invasion and malignancy is very strong.

Fibroma.—This tumor has been described as occurring in the rectum, but most if not all the examples have been merely inflammatory nodules.

A thrombosed hemorrhoid converted into a hard mass of fibrous tissue has often been mistaken for a fibroma.

Fig. 198.—Diffuse papillomatous tumor of rectum.

CARCINOMA OF THE RECTUM

The rectum is fifth in the list of primary seats of carcinoma, for over 5 per cent of all carcinomas occur there. Over 60 per cent of intestinal carcinomas are found in the rectum (Kaufmann). The three common sites are (1) the recto-sigmoid, (2) the ampulla, and (3) the anal ring. Cancer of the recto-sigmoid causes intestinal obstruction. A tumor in the ampulla does not do so, and the prognosis is therefore much better.

A point of vital importance to the surgeon is that carcinoma of the rectum (and this is true also of the colon) is as a rule of comparatively slow growth and only of moderate malignancy; extension beyond the bowel wall and distant metastases do not occur early. If, therefore, the diagnosis can be made early, as it can if only the patient can be educated so as to consult the surgeon during the early stage, the disease is quite amenable to surgical treatment. Unfortunately the golden moment is usually allowed to slip past unnoticed. In 1000 cases excised surgically Cuthbert Dukes found lymph node metastases in only 50 per cent. In 15 per cent of cases growth was still restricted to the rectal wall. In 35 per cent there was spread to the perirectal fat without lymph node metastases. In the majority of cases with lymphatic involvement only a few nodes are affected. It is not uncommon at autopsy to find the nodes completely free of cancer.

As with cancer elsewhere the disease is one of middle and late life, but youth offers no certain protection. The first case which I encountered as a house physician was in a boy of seventeen, and cases have been reported as early as the age of twelve. It usually proves fatal in from one

and a half to two years, but some cases survive for a considerably longer time. Death is commonly due to some complication such as perforation of the bowel, peritonitis, or acute intestinal obstruction.

The rectum is one of the regions of the body where the transformation of an innocent into a malignant tumor appears to be of fairly common occurrence. Carcinoma is frequently preceded by the development of an adenoma. These adenomata are often multiple but when one of them becomes malignant, the others tend gradually to disappear, so that it is in the early stages of carcinoma that this association is most likely to be observed. Lockhart-Mummery and Dukes have shown that a carcinoma of the rectum usually passes through three stages: first, the development of an epithelial hyperplasia, invisible to the naked eye, and affecting an
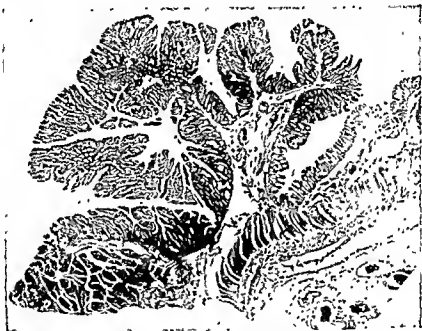
Fig. 199.—Malignant change developing in a papillary adenoma of rectum. The sudden transition from the innocent to the malignant state is well shown. × 10.

extensive area of the bowel; second, the appearance of a crop of sessile adenomata scattered over as wide an area as was affected by the initial hyperplasia; and third, the development of cancer either in one of these adenomata or in the neighboring epithelium. (Figs. 199, 200.) In my experience it is not uncommon for a single rectal adenoma removed adequately and completely to show microscopic malignant change in the mucosa but with no suggestion of invasion of the submucosa, a condition of carcinoma in situ. In such cases local removal seems to be sufficient.

The tumor commences in the mucous membrane and gradually invades the deeper structures. As in the stomach and the intestine it may take a massive form and project into the lumen of the gut. Usually, however, it tends partially to encircle the bowel, producing a more or less annular stricture, and only at a later date does the overlying surface be-
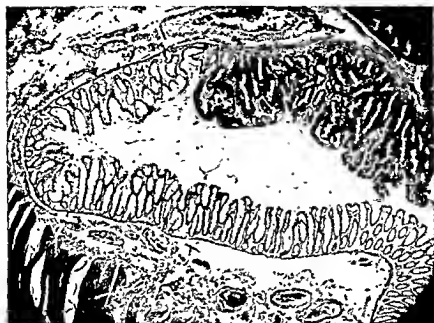
Fig. 200.—Transition from adenoma to carcinoma. Detail of Fig. 199. × 20.

Fig. 201.—Carcinoma of rectum. The mucosa is ulcerated and the walls greatly thickened.

come ulcerated (Fig. 201). The ulcer has the usual characteristics of a malignant ulcer; the edges are raised and indurated, and the ulcer is crater-like. With ulceration the symptoms at once become aggravated. Of

these the most noteworthy are a morning diarrhea which often alternates with constipation, hemorrhage, and toxic and cachectic symptoms which are due as much to the septic absorption as to the neoplastic process. The sudden development of internal piles and of a causeless sciatica are symptoms which should arouse suspicion.

Microscopically the picture is that of a characteristic adenocarcinoma or malignant adenoma. The transition between the normal and diseased mucosa is sudden and abrupt. The malignant cells not only replace the normal mucosa but penetrate the muscularis mucosae, and irregular acini or solid masses are formed in the submucosa, throughout which coat the

Fig. 202 — Carcinoma of rectum. Malignant glandular formation in deeper part of muscular wall. × 125.

disease may spread with ease. The cells in time make their way through the muscular coat and appear on the peritoneal surface (Fig. 202). In the rectum approximately 5 per cent of carcinomas are of the mucoid type, which has a greater tendency to recur than in mucoid carcinoma of the colon. Epidermoid carcinoma occurs in the anal canal, and metastasizes early to the inguinal nodes.

Methods of Spread.—There are three means by which carcinoma of the rectum may spread. These are (1) direct extension, (2) lymph spread, and (3) blood spread.

Direct Extension.—We have just seen that carcinoma commences as

a nodule in the mucous coat. At this stage it is freely movable on the underlying muscular coat. As the submucous and later the muscular coats become involved this mobility gives place to fixation. Extension takes place in all directions, but more particularly transversely. It may be stated as a general rule that by the time the growth has encompassed half the circumference of the bowel it will no longer be movable. From a series of careful observations W. E. Miles came to the conclusion that the involvement of the circumference of the bowel is a comparatively slow process, and that it takes at least a year for three-quarters of the circumference to be invaded.

When the carcinoma has penetrated all the layers of the rectal wall its further advance is temporarily delayed by a large lymph space which separates the rectal wall from the fascia propria of the rectum. It is not until this space is crossed and the fascia propria invaded that fixation to the surrounding structures such as the sacrum, prostate, bladder, uterus, or vagina can occur. As this invasion seldom occurs before the growth has involved three-quarters of the circumference, that is to say before a year has elapsed from the appearance of the earliest symptoms, it is evident that if direct extension were the only means of spread the operative treatment would involve little more than excision of the affected part of the rectum. Unfortunately other methods of spread occur at a much earlier date and involve a much wider area.

Lymph Spread.—From the nodes along the side of the rectum the lymphatics pass out in three directions, downwards, outwards, and upwards. The principal tissues involved in the *downward spread* are the skin around the anus, the external sphincter muscle, and the ischio-rectal fat. In the *lateral spread* the most important structures involved are the levatores ani muscles and the retrorectal nodes; at a later date the internal iliac nodes, the base of the bladder and seminal vesicles, or the cervix uteri and posterior wall of the vagina may be implicated. The *upward spread* is the most important of all, and at an early date may involve many or all the nodes in the pelvic mesocolon, and later the group of nodes at the bifurcation of the left common iliac artery. Needless to say involvement of these nodes cannot be detected by rectal examination.

Of these various structures the most vulnerable are the levatores ani muscles, the retrorectal nodes, the ischio-rectal fat, and the pelvic mesocolon. This will give some idea of the extent of the operation necessary for the extirpation of the disease.

Blood Spread.—Spread by the blood stream with metastases in the liver is, fortunately, a late manifestation of the disease. Occasionally, however, it occurs early. One of the largest livers I ever saw was the seat of carcinoma secondary to a growth in the rectum which was so small that it was nearly overlooked at the autopsy.

Prognosis.—The prognosis of cancer of the rectum depends partly on the degree to which it has spread, partly on the grade of histological differentiation. Dukes points out that from a study of the excised bowel the cases may be divided into three groups. (1) Group A in which the growth is limited to the wall of the rectum. (2) Group B in which there is extension of the growth to the extrarectal tissues but without metastases in the regional lymph nodes. (3) Group C in which the regional

lymph nodes are involved. Lymphatic metastases are usually not found until the growth has spread by direct continuity to the extrarectal tissues. Wood and Wilkie examined *all* the lymph nodes removed at operation together with the rectum in 100 cases. In 49 of these the nodes were entirely free of cancer, in 14 only one node was involved, and in 13 only two were involved. These facts form striking proof of the slow spread of cancer of the rectum to the lymph nodes. The prognosis in the A cases is very good, that in the B cases is slightly less favorable, whilst in the C cases the results of surgical treatment are very disappointing. Rankin and Broders find that the prognosis and likelihood of lymph node metastases depend on the histological grade of the tumor, but Dukes is of the opinion that this method is only reliable when the excised tumor can be examined, for the grade at the growing edge is apt to be higher than in the surface layers. It is from the latter that a biopsy specimen is likely to be taken. In mucoid carcinoma of whatever grade, the prognosis is very unfavorable, though this is not necessarily true of mucoid cancer elsewhere.

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THE GALL BLADDER AND LIVER

THE GALL BLADDER

Anatomy.—The normal gall bladder is 3 or 4 inches in length, with a capacity of about 1½ ounces. It is a thin-walled bluish sac, the inner surface of which has a velvety appearance, and is of a yellowish-green color. The bile in the gall bladder is darker and rather more viscous than that coming from the hepatic ducts, owing partly to the addition of mucus from the secreting epithelial cells lining the mucosa, partly to the concentration of bile which occurs within the organ.

The wall consists of a mucous membrane, a thick layer of plain muscle arranged somewhat irregularly and interspersed with fibrous tissue, and a peritoneal covering.

The usual anatomical description of the mucosa is that it is thrown into folds, but this conveys little to the mind until the gall bladder wall is viewed direct under that valuable instrument, the binocular dissecting microscope. When the fresh gall bladder, immersed in water, is observed by reflected light the picture is a remarkable and beautiful one. Tall graceful folds and membranes, gossamer-like in their delicacy, can be seen floating in the fluid like sea-weeds in a marine pool. The entire inner surface is divided by these membranes into a series of polygonal spaces, each of which resembles a little courtyard, surrounded by high though delicate walls. In microscopic sections the membranes, cut transversely, appear as villi (Fig. 203). They are not true villi, but the term may be allowed because of its convenience. This striking picture at once suggests that the idea of the gall bladder as a mere reservoir is absolutely untenable. Such a highly specialized structure can be for one purpose only, namely, absorption. In disease, as we shall see, the picture may undergo a complete change, and the delicate membranes become thickened, debased, and may finally disappear.

The gall bladder has no submucosa. In the normal organ no glandular structures pass from the mucosa into the underlying tissue, but in chronically inflamed gall bladders outpouchings of the mucosa may often be seen to pass for a varying distance into the muscularis and sometimes even into the perimuscular layer. These hernia-like outpouchings were described by Rokitansky in 1842, and are known as the Rokitansky-Aschoff sinuses. Their formation may be connected with increased intracystic pressure. Other duct-like structures are occasionally seen in the periphery of the wall, generally on the hepatic surface. They apparently represent accessory bile ducts, having a bile duct structure, and are known as true Luschka ducts. These various glandular structures in the deep layers of the gall bladder wall must not be mistaken for carcinomatous formation.

The efferent lymphatics of the gall bladder drain into the cystic gland, situated at the junction of the neck of the bladder and the cystic duct. Thence the flow is into a number of lymph nodes along the common bile duct. Under normal circumstances the lymph flows to the receptaculum chyli; but when the passages are occluded by inflammation it may pass to the pancreatic plexus, and may thus convey infection from the gall bladder to the pancreas.

The gall bladder has a double nerve supply, partly cerebrospinal from the vagus, partly sympathetic from the ninth dorsal segment. The vagus is the motor and secretory nerve; it inhibits the sphincter. The sympathetic is the sensory nerve to the gall bladder, and the motor nerve to the sphincter. The nerve supply is of great importance in explaining the symptomatology of gall bladder disease, for the symptoms are usually
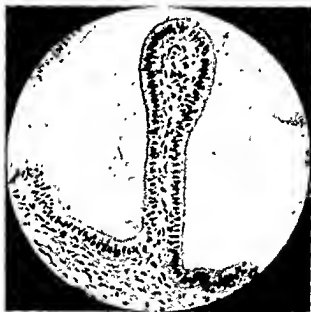
Fig. 203.—Normal gall bladder showing fold covered by tall columnar epithelium × 500

referred to other organs such as the stomach. Inflammation of the gall bladder acts reflexly through the vagus and tends to cause hyperchlor- hydria and regurgitation. In cases where the inflammation is more severe the sensory stimulus is greater, and a sympathetic reflex through the ninth thoracic segment results in pylorospasm.

The cystic, hepatic and common bile ducts are merely fibro-elastic tubes and contain practically no plain muscle, although they are abun- dantly supplied by nerve fibers. The biliary colic which accompanies the passage of gall stones is therefore not caused by muscular spasm but is probably due to distension of the duct with pressure on the nerve endings.

Physiology.—The gall bladder is not a mere passive reservoir for the bile, converting the continuous flow from the liver into an intermittent flow into the duodenum. Its highly specialized structure would be mean- ingless for such a purpose. Rous and McMaster have shown experi-

mentally that the gall bladder concentrates the bile by a process of absorption; the bile may be concentrated in this way as much as 10 times. The idea is not a new one, for in 1847 Virchow suggested that the function of the gall bladder was absorption rather than storage. Halpert believes that the bile is absorbed in toto, and that the bile which enters the gall bladder does not again leave it by the cystic duct. Boyden, however, has shown that a "fat" meal, *i. e.*, one consisting of egg-yolk and cream, causes the gall bladder of the cat to empty. This normal emptying apparently does not occur during pregnancy (Mann and Higgins).

When a solution of magnesium sulphate is applied to the duodenal mucosa of an animal a flow of bile is obtained. Meltzer explained this phenomenon by the "law of contrary innervation"; the muscle of the gall bladder was supposed to contract, while the sphincter of Oddi at the opening of the bile duct relaxed. This is the basis of Lyon's method of "non-surgical drainage" of the gall bladder by means of the duodenal tube. The theoretical conception underlying the Lyon test has been much criticized, and it is doubtful if the contents of the gall bladder can really be obtained in this way. It appears that magnesium sulphate and many other substances when introduced into the duodenum excite a flow of bile from the biliary passages in the liver. As pathological elements such as pus cells which may be present in the gall bladder are also likely to be found in the bile from the hepatic ducts, the test still seems to have some practical value.

Graham's visualization test is really a test of the concentrating power of the gall bladder. When tetraiodophenolphthalein is given by mouth it is excreted by the liver in the bile. If the gall bladder is functioning normally the dye will become so concentrated as the result of absorption of bile that the outline of the gall bladder becomes visible in an X-ray picture. Disease of the gall bladder wall interferes with absorption, so that the organ is not visualized. It is obvious that if anything interferes with the entrance of the bile into the gall bladder, there will be no visualization of the organ.

CHOLECYSTITIS

Etiology.—Cholecystitis or inflammation of the gall bladder may be acute or chronic. There is still much difference of opinion regarding (1) the bacteria concerned, (2) the route of infection.

1. The *bacteria* found in *chronic* cholecystitis are varied. It used to be thought from the work of Rosenow and A. L. Wilkie that nonhemolytic streptococci were the essential causal agent. Wilkie overcame the inhibitory effect of the bile by making cultures from the cystic lymph gland which drains the gall bladder. Other workers have failed to confirm these results. Thus Williams and McLachlan, working like Wilkie in Edinburgh University, found B. coli in 20 per cent of cases, but streptococci in only 16 per cent, nor did the presence of bile seem to make much difference. Magner and Hutcheson obtained streptococci in 37 per cent of cases, B. coli in 28 per cent, and staphylococci (probably contaminants) in 37 per cent. In *acute* cholecystitis, especially in fulminating cases, B. welchii and other anaerobic organisms may be the principal infecting agent. It is probable that they come from the liver. B. welchii

may also be found in chronic cholecystitis. Gordon-Taylor and Whitby found it in 9 per cent of gall bladders removed surgically, and in 13 per cent of gall stones removed postmortem.

2. The route of infection may be (a) by the blood stream, (b) from the liver. Ascending infection from the duodenum does not occur.

(a) *Hematogenous infection* is probably the common method. The inflammatory lesions of chronic cholecystitis are most marked in the deeper part of the wall.

(b) *Hepatogenous infection* may occur in two ways. (1) Large numbers of bacteria are carried by the portal vein from the bowel to the liver to be destroyed. If they escape destruction they are excreted in the bile, and may infect the gall bladder. The common localization of the infective foci in the outer part of the wall does not support the idea of an infection from the mucous surface. (2) The spread may be from the liver to the gall bladder via the lymphatics, as suggested by Evarts Graham. It is true that evidence of hepatitis is often found in the neighborhood of an inflamed gall bladder, but it must be remembered that the infection may have spread from the gall bladder to the liver. Ligation of the cystic or common bile duct producing biliary stasis favors prompt infection of the gall bladder wall by anaerobic organisms which appear to pass from the liver to the gall bladder by direct extension (Andrews and Hrdina). The anaerobic organisms found in many cases of cholecystitis correspond to the normal flora of the liver, which is intestinal in origin.

Doubt, well summarized in a paper by Andrews, is being expressed regarding these generally accepted bacteriological views. When inflammation in the gall bladder is compared with inflammation in other hollow abdominal organs such as the appendix and the urinary bladder some striking differences become apparent. In an acutely inflamed appendix there is close correlation between the pathological changes and the clinical symptoms, and bacteria are present in enormous numbers. In acute cholecystitis the histological picture is rarely one of acute suppuration, and there is little difference between the bacterial content of acute and quiescent cases. Moreover it is not uncommon to find bacteria derived from the liver in cultures of the wall of the normal gall bladder. There is, therefore, much to be said for the view that in the ordinary case of gall bladder inflammation bacterial infection plays but a minor rôle. Another curious feature about the gall bladder, pointed out by McKibbon and McDonald, is that polymorphonuclear leucocytes are frequently present in one or more layers of the organ without any other evidence of inflammation; in other words, they may occur in an apparently normal gall bladder. They do not indicate inflammation, and appear to be metabolic in function.

Occlusion of the cystic duct is probably the most important single factor in the production of cholecystitis. The lumen of the normal duct is small, its wall is thick and deeply infiltrated with sinuses, so that a slight degree of inflammation will cause narrowing or closure of the duct. The intensity of the ensuing inflammation depends on the composition of the imprisoned bile. Womack and Brickner have shown that when the cystic duct is occluded after the gall bladder has been emptied of bile and washed with saline there is no change in the wall. When the gall

bladder is not emptied, occlusion of the duct results in moderate edema, round cell infiltration and fibrosis. When the bile is replaced by a solution of dried bile double the concentration of that of normal bile, the gall bladder wall undergoes complete necrosis, although when the cystic duct is open the changes are slight and transient. It would appear, therefore, that while cholecystitis may be due to bacterial invasion in some cases, it may also be due to chemical irritation by bile when the cystic duct is closed. This agrees with Mann's observation that acute cholecystitis can be produced by introducing Dakin's solution into the gall bladder.

Denton has pointed out that in some cases the condition appears to be one of infarction rather than inflammation. The veins of the gall bladder are much more closely incorporated with the cystic duct than is the cystic artery, so that a large stone impacted in the duct may close the veins before the artery, and thus lead to edema, congestion and infarction. In such cases the onset of symptoms is very sudden, the tensely distended gall bladder is bright or dark red, and the microscopic appearance is one of edema, venous distension, and hemorrhage. One of my cases, however, presented a typical infarcted appearance, with a very acute history of less then 24 hours, and multiple stones in the bladder, but at operation no stone was found in the duct.

Morbid Anatomy.—The condition of the gall bladder will naturally vary with the nature of the inflammation. The inflammation may be acute or chronic. The chronic inflammation may or may not be preceded by an acute attack.

Cholecystitis is frequently associated with gall stones, but may occur without them. The longer the condition has lasted the more likely is it to be complicated by calculi. MacCarty found that in 365 cases of cholecystitis there were stones in 69 per cent of acute catarrhs, in 76 per cent of chronic catarrhs, and in 93 per cent of the advanced chronic inflammations.

Andrews points out that lesions such as ulcers reported as pathological are often due to mechanical injury by clamps and forceps in the course of removing the gall bladder. After the gall bladder has been removed from the body there is rapid autolysis of the mucosa due to the action of bile, and this may be complete within five or six hours. Unless the gall bladder is opened, emptied of bile, and placed in a fixative, the mucosa may show degenerative changes which may lead to error, or the epithelium may be completely lost. Sections taken from different parts of the organ may differ widely in their appearance, and the inflammatory infiltration may be markedly patchy. Fixation may lead to a great change in the gross appearance, so that a gall bladder which was thick walled at operation may appear to be almost normal on section; this is because much of the thickening is due to edema, and the edema fluid may be lost in the process of fixation and dehydration. The normal mucosa contains large numbers of round cells. When these various facts are taken into consideration it becomes evident that laboratory reports on the gall bladder are apt to be misleading, and that there may be little correlation between such reports and the condition of the patient.

Acute Cholecystitis.—In acute inflammation the wall of the gall bladder is thickened, the serous surface is congested and may be covered

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by a fibrinous exudate, and the mucosa is of a bright red color. When obstruction of the cystic duct is complete the lumen of the viscus may be distended with what appears to be a purulent fluid, so that the condition is known as *empyema of the gall bladder* (Fig. 204). If, however, the creamy contents are examined microscopically they will be found to consist not of pus but of an emulsion of cholesterol crystals or of calcium carbonate.

The *microscopic picture* presents a striking contrast to the acutely inflamed appendix because of the remarkable absence of the abundant purulent exudate which is characteristic of acute appendicitis. Polymorphonuclears are relatively few in number, and the exudate is most marked in the outer layers of the wall. The epithelial lining may be astonishingly intact even when the inflammation is extremely acute. The most striking feature is a marked inflammatory edema. This may be observed in the mucosa, but it is usually most abundant in the serous and subserous layers. Edema is responsible for most of the thickening of the wall. It is apparent that acute cholecystitis is in a different category from ordinary inflammation due to bacterial irritants. In some of my material the picture has been characterized by an abundant purulent infiltration. In such cases bacteria evidently assume a predominant role, and the bacterial count in the bile is enormously increased.

Chronic Cholecystitis.—Chronic cholecystitis may be the result of acute inflammation, or it may come on gradually and insidiously. The latter cases are apparently due to infection with some low grade irritant such as Streptococcus viridans.

Fig. 204.—Empyema of gall bladder. A dilated and thickened gall bladder which is now acutely inflamed and distended with pus.

The gross appearance varies considerably. The external surface no longer has an appearance of thinness, but is opaque and may be yellow owing to an accumulation of subserous fat. The gall bladder may be dilated or contracted, depending on the relative balance of obstruction and inflammation. If obstruction occurs before the chronic inflammatory changes have had time to produce thickening, the organ may be dilated and relatively thin-walled. In other cases the contraction and thickening may be extreme.

When the gall bladder is opened the condition again varies greatly. The mucosa may be edematous and swollen. Under the dissecting microscope the change from beautifully thin to thick swollen villi is very strik-

ing. These become debased and eventually disappear. When gall stones are present the surface may become eroded, but it is remarkable how intact the epithelium may be in the worst looking gall bladders. The stroma of the mucous membrane (called the submucosa by some writers) is plentifully infiltrated with inflammatory cells. These are mostly of the mononuclear wandering type, lymphocytes and plasma cells, with polymorphonuclears when the inflammation is more acute. In the later stages there may be an abundant formation of granulation tissue with numerous fibroblasts and other fixed connective tissue cells (Fig. 205). Congestion may be marked, but hemorrhages as a rule are not common.

As a result of the inflammation, possibly because of increased intracystic pressure, there may be outpouchings of the mucosa into or through the muscularis. These are known as Rokitansky-Aschoff sinuses. When the section is cut obliquely, so that the connection with the mucosal sur-

Fig. 205.—Chronic cholecystitis. The folds of mucosa are thickened, edematous, and contain dilated lymphatics. The epithelium is quite intact. × 300.

face is not apparent, they may be mistaken for carcinoma. Sometimes there is apparently a proliferation of epithelium and a formation of new glands, a condition known as *cholecystitis glandularis proliferans* (Fig. 206). A mass may be formed on the serous surface, or the proliferation may take place on the surface of the mucosa, forming a papillary projection or papilloma.

Even more important are the changes in the muscular and serous coats, which may show marked lesions although the mucosa appears quite normal. In both of these the characteristic lesions are dilated capillaries and focal collections of chronic inflammatory cells, although sometimes the infiltration is more diffuse. Edema is often a marked feature, and the subserous coat is much thickened. Large collections of fat may frequently be observed in the subserous and muscular coats. As fibrosis replaces the muscular and elastic tissue is entirely replaced by scar tissue, so that the

gall bladder is converted into an inert bag. As a result of the scarring the inner surface becomes reticulated and honey-combed, presenting an interlacing network of fine bands (Fig. 207) but eventually these also disappear and the lining becomes perfectly smooth.

The thickening of the wall may be extreme in degree, and the cavity is often much contracted. In one case which came under my notice

Fig. 206.—Cholecystitis glandularis proliferans. × 33.

Fig. 207.—Chronic cholecystitis with extreme degree of scarring.

Fig. 208.—Drainage tube left in gall bladder for three years. Extreme thickening of wall and contraction of cavity.

a piece of drainage tube had been left in the gall bladder by mistake three years previously. The walls of the bladder were half an inch thick, and were so contracted upon the tube that no trace of lumen was left

(Fig. 208). A similar condition is often seen where the gall bladder has been full of calculi for a long time.

Fig. 209.—*Advanced stage of chronic cholecystitis. The reticulation of the wall is extreme. A large stone is impacted at the neck of the bladder. The tube at the side contains the clear watery contents.*
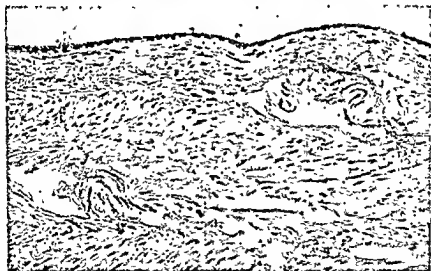
Fig. 210.—Hydrops of the gall bladder showing obliteration of the folds The low epithelium is the only part of the mucosa remaining. × 125.

When the scar tissue involves the cystic duct the resulting obstruction gives rise to great dilatation of the gall bladder, the walls of which are very thin. The cavity is filled with clear, colorless, watery fluid which

has been secreted by the remnants of the mucosa (Fig. 209). Owing to the obstruction of the cystic duct the gall bladder contains no bile. In such cases there is complete loss of the villi which are the absorbing mechanism of the gall bladder, and the wall becomes as flat and feature-less as that of the urinary bladder (Fig. 210). The condition is known as *hydrops* of the gall bladder. If a pyogenic infection is superadded the bladder becomes filled with pus, an *empyema* of the gall bladder. The latter condition may of course occur in acute cholecystitis should the cystic duct become obstructed. The state of the gall bladder depends largely upon the balance between infection and obstruction. If infection be marked and obstruction slight or absent, the bladder will be small and thick-walled. If infection be slight but obstruction marked, the blad-der will be dilated and thin-walled.

CHOLESTEROLOSIS OF THE GALL BLADDER

The Strawberry or Lipoid Gall Bladder.—One of the most interest-ing of the early results of chronic inflammation is the curious appearance first described by Moynihan, and to which the name strawberry gall bladder was given by MacCarty, although lipoid gall bladder is more scientific and equally descriptive. The reddened mucosa is studded with

Fig. 211.—Strawberry gall bladder.

tiny yellow specks, suggesting the seeds of a ripe strawberry. Sometimes the entire gall bladder is involved (Fig. 211), at other times only one portion.

The condition is best studied under the binocular dissecting micro-scope. The graceful, fragile, gossamer folds of mucosa are completely altered in appearance, being loaded down by dense, yellow, opaque masses much as a delicate birch tree might be weighed down by a load of

Fig. 212.—Mucous membrane of a strawberry gall bladder at an early stage. The patches of lipoid are whitish in color. Viewed through the binocular dissecting microscope.

Fig. 213.—Deposits of lipoid stained with osmic acid.

snow (Fig. 212). Sometimes the yellow material is confined to the summit of the ridges, sometimes it can be traced down into the depth of the recesses. In the severe cases the distribution is widespread. In the milder

cases it is more patchy, picking out a fold here and there, and giving the mucosa the appearance of a mountain ridge retaining only an occasional patch of the winter's snow. Before it is fixed in formalin the material can be lifted up in long strings by means of a needle as if it consisted of molasses.

The yellow material gives the usual reactions for fat. It is soluble in alcohol and chloroform, so that it cannot be seen in paraffin sections. It stains bright red with Scharlach R (Fig. 214), and black with osmic acid (Fig. 213). In these respects it behaves like neutral fat, which is an ester of glycerine, and which is sometimes found in large amount in the subserous tissue and in the deeper layers of the fibrous coat of the diseased gall bladder.

Although evidently of lipoid nature, it differs from ordinary fat in some important particulars. Of these the most noteworthy is its behavior when viewed in frozen sections by polarized light under crossed Nicol's prisms. Under these conditions neutral fat is quite invisible, but the lipoid of the strawberry gall bladder stands out in the most beautiful and brilliant manner, shining with a silvery radiance which is accentuated by the surrounding darkness. It is sometimes in the form of granular amorphous masses, frequently it appears as innumerable tiny needle-shaped crystals, and occasionally as bright Maltese crosses standing out against a black background.

The lipoid therefore displays the properties of an ester of cholesterol, and is of similar nature to the lipoid occurring in the adrenal cortex and the corpus luteum of the ovary. In this connection the well known relation between pregnancy and gall stones may be recalled to mind.

When cholesterol crystals are treated with concentrated sulphuric acid they turn a bright carmine red; with the ester the resulting color is a terracotta brown. We have succeeded in applying this test to frozen sections of the gall bladder, and the lipoid displays the same reddish brown color; this is a chemical test developed in the tissues.

The lipoid may be demonstrated without the use either of special staining methods or of the polarizing microscope. When a frozen section of a strawberry gall bladder is examined under an ordinary microscope with the diaphragm well closed, the lipoid is seen as dark, almost black, masses. Under the high power the acicular crystals can be made out with great distinctness.

Chemical estimations made in my laboratory show that the cholesterol content of the mucosa of the strawberry gall bladder is enormously in excess of that found in the normal organ. In one case it was sixty times the normal.

The distribution of the lipoid varies. In most cases it is confined to the surface epithelium, lying for the most part at the base of the cells. In other cases it is scattered throughout the stroma, both free and contained within wandering cells (Fig. 215). In a few of our cases a very significant appearance was observed. The lipoid had collected in great masses in a villus, which now resembled a papillomatous process the stalk of which had become so attenuated that separation seemed inevitable. Should this occur we would have a foreign body composed of cholesterin and albuminous material lying in the cavity of the gall bladder, and forming an ideal

Fig. 214.—Polypoid mass of cholesterol ready to separate. Early case of strawberry gall
bladder. Stained with Scharlach R.

nucleus for the formation of further deposits. The condition is well shown in Fig. 216.

It really appears that here we have a gall stone actually being formed in the gall bladder mucosa. How common a mode of formation of calculi this may be can only be determined by further investigation. Chauffard comes to a similar conclusion. He found that small biliary calculi may originate inside the villi as minute collections of cells surrounded by cholesterol; these are shed, grow, and ultimately become faceted.

Pathogenesis.—The mode of production of the strawberry gall bladder is not certain. It is generally believed that the cholesterol of the bile is absorbed through the epithelium lining the gall bladder. My own observations support this view. Elman and Graham, however, believe that it is excreted instead of absorbed by the gall bladder. They found that
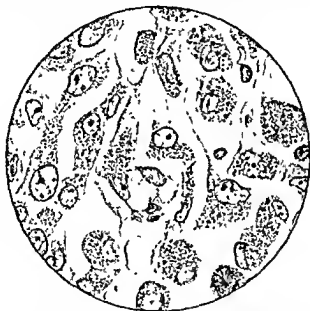
Fig. 215.—Inflammatory cells packed with lipoid granules.

ligation of the cystic duct increased the amount of cholesterol in the bile in the gall bladder, and they believe that inflammation accelerates the excretion. Blaisdell, on the other hand, obtained deposits of cholesterol in the mucosa and submucosa of the gall bladder by feeding an animal with cholesterol and thus producing a condition of hypercholesterolemia, but not when the cystic duct was first tied. This suggests that the deposits were the result of absorption. Every paper that comes out seems to contradict its predecessors. Thus Patey found that tying the cystic duct in a cholesterol feeding experiment did not prevent the formation of cholesterol deposits in the gall bladder wall. Perhaps the closest approximation to the truth is that expressed in the findings of Wilkie and Doublelet, who showed that the direction of passage of cholesterol through the gall bladder wall depends on the blood-bile cholesterol ratio. In a normal dog with the cystic duct tied when the cholesterol concentration of the

bile is lower than that of the blood, cholesterol passes from the blood through the gall bladder mucosa into the bile; when it is higher the passage is in the opposite direction.

Two facts somewhat detract from the surgical interest of cholesterolosis of the gall bladder. The first is that well marked lipoid deposits can occur in a gall bladder which is in other respects normal. The second is that there is no convincing evidence that these deposits can cause symptoms or that they are of any clinical significance.

The Stasis Gall Bladder.—German observers have called attention to the condition of *Stauungsblase* or stasis gall bladder. It is a fact well known to surgeons that a patient with gall bladder symptoms may be found at operation to have neither cholecystitis nor calculi. These cases have been studied by many workers, more particularly by Aschoff, Berg,
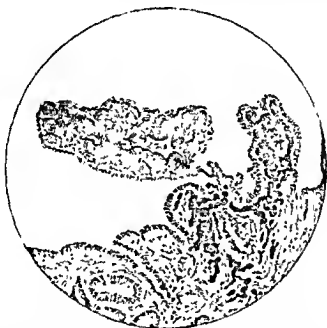
Fig. 216.—*Masses of lipoid in the stroma. The surface epithelium is intact. Stained with Scharlach R.*

and Westphal. Atonic and hypertonic varieties have been described. In the atonic variety the gall bladder wall is thin and lax, in the hypertonic it is thick and the bladder is distended. In both there is stasis of bile and a tendency to the formation of stones. Westphal has shown that the hypertonic, or, as he calls it, the hyperkinetic variety, is due to vagal spasm of the neck of the gall bladder and the sphincter of Oddi, a condition which is frequently present in the early stages of pregnancy. This may be a factor of importance in determining the formation of calculi in pregnant women.

GALL STONES

Gall stones may be formed in the gall bladder or in the bile passages. They may be single or multiple. The single are non-faceted, the multiple usually faceted. They are made up of cholestrol and calcium bili-

rubin, with frequently a framework of disintegrated cells (Fig. 220). For a full realization of the importance of distinguishing between the different

Fig. 217.—Metabolic stone; radiate structure of cholesterol center.

Fig. 218.—Mixed stone showing concentric structure.

kinds of calculi we are indebted especially to the work of Aschoff and Bacmeister. Two main types of stone may be recognized, the metabolic or aseptic stone, and the inflammatory or septic stone.

Fig. 219.—Gall stones in a chronically inflamed gall bladder. The faceted calculi are of the infectious type, but are covered by a layer of cholesterol.

1. The *metabolic stone* is large, oval, single, white, composed entirely of cholesterol, and therefore known as the cholesterol solitaire. Aschoff calls this a metabolic stone because it is apparently formed solely as the result of disordered liver metabolism. Cholesterol is kept in solution by the bile acids, but the solubility is dependent not only on the amount but on the relative proportion of the acids. Any disturbance in the acids, and increase in the cholesterol, may be followed by precipitation of the latter. The stone is distinguished by its radiate structure (Fig. 217), as opposed to the concentric structure of the septic or inflammatory stone. Frequently it gives rise to no symptoms, and is only found by accident at autopsy. It is a silent stone, and as a rule the gall bladder shows no evidence of inflammation. It may, however, become impacted in the neck of the gall bladder, and the acute stasis which results is apt to be followed by infection. Should the stone then roll back into the bladder and allow the bile to re-enter, a deposit of bilirubin calcium is laid down upon the cholesterol solitaire, with the result that what is termed a combination stone is formed, a
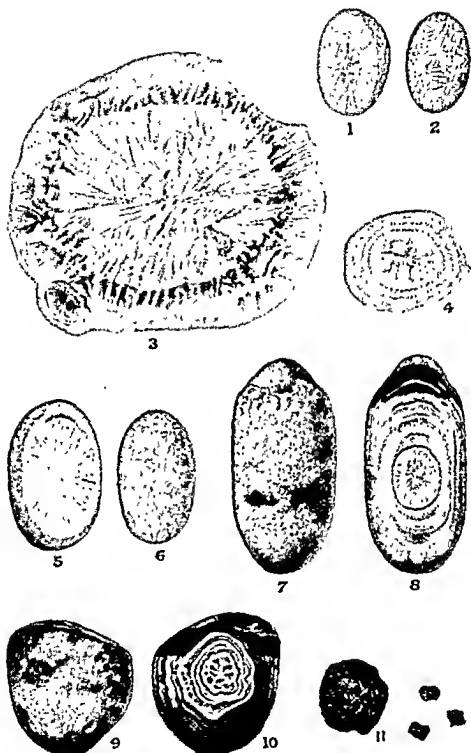
Fig. 220.—Varieties of gall stones. 1 and 2, Radiate pure cholesterol stone. 3 and 4, Centers of pure cholesterol stones. 5, 6, 7 and 8, External and cut surfaces of two combination stones. Shows the radiate cholesterol center surrounded by rings of cholesterol pigment-chalk. 9 and 10, Common faceted cholesterol-pigment-chalk stone. Concentric laminae throughout. 11 and 12, Pure pigment stones, often called mulberry calculi. (Modified from Bacmeister, from Rolleston and McNee: Diseases of the Liver, Gall-

combination of the metabolic and the inflammatory types. There is this great difference between a pure cholesterol stone and a combination stone; the pure stone is solitary whilst the combination stone, being partly infective in origin, is nearly always associated with the septic type of multiple calculi. The formation of a pure cholesterol stone is favored by such factors as high blood cholesterol (and, therefore, high bile cholesterol), and by stasis in the gall bladder. We have seen, however, that although a high blood cholesterol conduces to the formation of a cholesterol solitaire, it by no means follows that it will be high at the time the stone is removed.
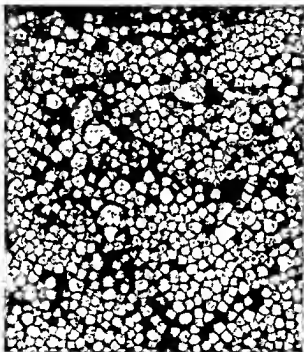
Fig. 221.—Multiple faceted calculi removed from one gall bladder. All the stones are of about the same age.

Before leaving the subject of the metabolic stone, mention must be made of another variety, much less common and more difficult to understand. This is the *pure pigment stone*. These are multiple, about the size of a grain of rice, black in color, and of a hard brittle consistence. They contain no cholesterol. These are the stones which so frequently complicate hemolytic jaundice, but other factors concerned in their origin are, as far as I am aware, still unknown.

2. *The Infective or Septic Stone.*—These are the faceted cholesterol-pigment-calcium stones which on section present not a radiate but a characteristic concentric arrangement of laminae (Fig. 218). All the stones of one family are about the same size, but there may be two and sometimes even three families (Figs. 219, 221). In addition, there may be one or more large combination stones. If the crystalline material is removed

by means of chloroform or ether a protein framework is left which shows the same concentric lamellation as the stone. This is never seen in the pure cholesterol stone. It is evident, therefore, that they are formed in a medium rich in protein, whilst the pure cholesterol stone is formed in a medium poor in protein. This provides us with a clue to the way in which these stones originate. As the result of inflammation of the gall bladder a mixture of pus, mucus, bacteria, and epithelial debris is poured out. During on acute attack the gall bladder is more or less a closed cavity, but as the swelling at the neck subsides bile again enters, and around the little nuclei of organic matter are deposited layers of cholesterol and bilirubin calcium. In this manner the family of faceted septic stones is formed.

Gall stones may give rise to symptoms either during their passage along the cystic and common ducts or during their residence in the gall bladder. As regards biliary colic, it is true of the gall bladder as of the kidney that little stones like little dogs, make the most noise. A large stone is more likely to remain in the gall bladder, more or less silent. Gall stones of the ordinary type are always associated with inflammation of the gall bladder. The cholecystitis is usually chronic in character, but not infrequently an acute attack may be superadded. Reference has already been made to the nervous mechanism by means of which the pain and discomfort in the gall bladder are referred to the stomach.

As a result of the chronic inflammation the wall of the gall bladder becomes greatly thickened, and its cavity may become so contracted that there is room for little else in it besides the calculi. This truth is expressed in the general rule known as *Courvoisier's law*, that in jaundice due to pressure on the common bile duct from without, as from cancer of the head of the pancreas, the gall bladder is distended, whereas in jaundice due to impaction of a stone in the common duct the gall bladder is usually contracted. A much dilated gall bladder, however, may contain stones. Thus a stone may be impacted in the cystic duct, so that the gall bladder becomes distended with mucus and yet at the same time it may contain numerous calculi.

The stone may be embedded in a deep pocket, through which perforation may occur. The danger of the stone perforating the wall of the gall bladder has already been referred to. Should the perforation occur into the transverse colon the stone is likely to be passed without trouble. When the perforation is into the small bowel the stone, if at all large, is apt to become impacted some distance above the ileocecal valve. In one of our cases impaction at the lower end of the small intestine with symptoms of acute abdominal obstruction was caused by a stone the size of a pigeon's egg. It is difficult to understand how so large and hard an object could pass for such a long distance along the small bowel without causing such a degree of spasm as completely to stay its course. In most of the recorded cases, however, the obstruction has been at the same site.

Etiology.—The problem of gall stones is the problem of calculus formation in general, and cannot yet be said to be solved. There are three factors which have to be considered. It does not follow that any one of them must be given pride of place in every case, for there may well be various conditions which will result in a precipitation of the solid constituents of the

bile. The three factors are (1) bacterial infection, (2) stasis of the bile, and (3) a high cholesterol content of the bile.

1. *Infection.*—Of these three factors infection is probably by far the most important. Moynihan puts it in characteristically epigrammatic fashion: "every gall stone is a tombstone erected to the memory of the organisms dead within it; but sometimes the organisms are buried alive." The brilliance of the epigram, however, must not mislead us into applying it to every case of gall stones.

Experimental injection of virulent bacteria into the gall bladder does not give rise to the formation of calculi, but to an acute purulent inflammation which destroys the mucosa, a condition in which bile and bile-pigments are entirely absent. The introduction of sterile foreign bodies is also unaccompanied by the formation of stones. When, however, attenuated cultures are used, a mild inflammation is set up, and if this is accompanied by partial obstruction of the cystic duct owing to swelling of the mucosa, a calculus may result.

Infection is an important factor in determining the precipitation of substances usually held in solution. When a specimen of bile is inoculated *in vitro* with a culture of B. coli, precipitation of the cholesterol and of the pigments occurs. This is probably due to interference with the bile salts upon the presence of which the solubility both of the cholesterol and of the bile pigments depends. '

Typhoid fever is a common cause of infection of the gall bladder, and in such cases the bacilli are often found in large clumps. Moynihan quotes a case in which the clumping suggested that a gigantic serum reaction had taken place in the gall bladder. Living typhoid bacilli may be found in the interior of the gall stones long after the original attack. Lewellys Barker mentions that living bacilli were found in a gall stone removed 35 years after an attack of typhoid fever.

2. *Stasis of the Bile.*—It is obvious that precipitation of the solids of the bile is much more likely to occur in conditions of stagnation than when there is a free outflow of bile. Such stagnation may be due to obstruction, a sedentary mode of life, muscular atony, interference with the innervation of the gall bladder, etc. Observations on the emptying effect of a "fat" meal by Mann and Higgins showed that stasis of the gall bladder is a normal accompaniment of pregnancy in the animals which they examined.

3. *The Cholesterol Content of the Bile.*—Two of the conditions most frequently associated with calculus formation, namely typhoid fever and pregnancy, are characterized by a great increase in the cholesterol content of the blood and therefore of the bile. Gall stones are much commoner in the female sex (the proportion being 3 or 4 to 1), especially in stout women who have borne children, so that the old adage "fat, female, forty" in relation to gall stones contains much truth. But here again the danger in the past has been to overlook the importance of the gall bladder itself. As we have already seen, the wall of the gall bladder may, under certain conditions, present an increase of the cholesterol content beside which any increase in the cholesterol in the bile fades into insignificance, and it is more than possible that in many cases the initial stage of calculus formation may take place in the gall bladder mucosa (Fig. 222).

Cholesterol is held in solution in the bile in a series of loose and firm chemical complexes with the bile salts. Most of the complexes are broken up by relatively slight influences such as dialysis (Andrews). If by some means the bile salts are removed, the cholesterol is precipitated. There is no differential absorption of cholesterol and bile salts from the normal gall bladder. The infected gall bladder, on the other hand, absorbs bile salts rapidly but cholesterol very slowly if at all. In cases of cholesterol stones the bile acid content of the bile is always low.

The factors which make for the formation of gall stones are apparently periodic rather than continuous in their mode of action. A collection of gall stones from one case are usually of the same size and type. They are all
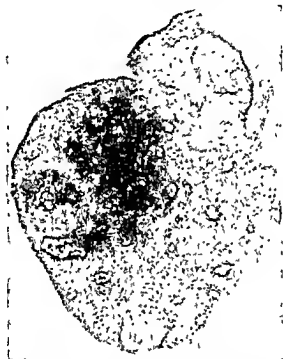
Fig. 222.—Deposits of cholesterol in wall of gall bladder. These polypoid masses may form the starting point of calculi.

apparently born about the same time. Not infrequently different families may be recognized, but the various members of each family are all of the same birth.

The two factors most liable to periodic fluctuation are the cholesterol content and infection. The cholesterol content of the blood and of the bile will rise with each pregnancy, only to fall to normal in the intervals. Infection, again, is probably often periodic. The kidney in Bright's disease, the heart valves in endocarditis, may be the seat of recurring infections, after each of which the organ is left more and more damaged. So also with the gall bladder. The profoundly altered gall bladders which we often encounter are not as a rule the result of a single infection, but represent the cumulative effect of many such attacks.

CARCINOMA

The gall bladder is peculiarly liable to malignant disease. A possible explanation of this lies in the relation of cancer to gall stones. In from 80 to 90 per cent of gall bladder carcinomas calculi are present. As might be expected, the disease is four or five times more common in women than in men. Possibly the fact that methylcholanthrene, one of the most powerful chemical carcinogens, is derived from cholic acid in the bile, is of importance.

Formerly it was believed from experimental evidence that the introduction of gall stones into the gall bladder of an animal would result in carcinoma. This is a mistake. Burrows has shown that this procedure

Fig. 223.—Carcinoma of neck of gall bladder; early strawberry appearance in mucosa.

will cause rapid and extensive proliferation of the mucosal glands with eventual penetration into the liver and omentum, a remarkable example of cholecystitis glandularis proliferans which in the past has been mistaken for carcinoma.

The disease may begin in any part of the gall bladder, but the parts most commonly affected are the fundus and the commencement of the cystic duct (Fig. 223). The usual form is an adenocarcinoma, but in rare cases an epithelioma may be present, arising probably from a metaplasia of the columnar to squamous epithelium.

The same varieties of growth are found as have already been studied in the stomach and intestine, namely the papillomatous form and the diffuse infiltrating form. The latter is the more common, and gives rise to great thickening of the wall from a scirrhous growth. The liver is

invaded early, and jaundice is one of the most constant features. In the papillomatous form the gall bladder is filled with a soft mass, which may occasionally become converted into a colloid cancer.

Metastases occur to the glands along the common bile duct. Tumor cells may pass via the lymphatics through the falciform ligament to the umbilicus, where they form secondary nodules.

Carcinoma of the bile ducts may affect the common duct, giving rise to complete obstruction, or more rarely it commences in a duct within the liver, where it constitutes one form of primary carcinoma of the liver. It appears as a small, hard, white mass, which may be mistaken for a calculus.

Liver Death.—In 1924 Heyd directed attention to a group of cases in which operation on the biliary tract is followed by death which comes unexpectedly, many times like a bolt from the blue. To this condition Heyd gave the name of "liver death," although as a rule no lesions of the liver can be found at autopsy. The conception has met with a good deal of criticism, but the evidence in support of it appears to be adequate. The whole matter is discussed at length in Boyce's excellent monograph on "The Role of the Liver in Surgery." After an uncomplicated operation such as cholecystectomy there may be a rapid rise of temperature to 105° or 107° F., with death in from 36 to 48 hours. The patient manifests great nervousness, a quick pulse, and a low blood pressure. In the very acute cases no liver lesions may be found, but in cases where death is delayed there may be fatty changes or focal necrosis of liver cells. The condition has been reproduced, although with difficulty, in the experimental animal. In some cases a renal element may be added, the so-called *hepatorenal syndrome* in which degeneration and necrosis of the cells of the convoluted tubules of the kidney are accompanied by oliguria and anuria. Liver and liver-kidney deaths have followed traumatic injury to the liver, burns and experimental obstruction of the biliary tree and ligation of the hepatic artery; the syndrome may also occur in thyroid disease and intestinal obstruction.

Various hypothetical toxins produced by operation have been blamed for the disaster, but Boyce suggests an underlying hepatic dysfunction which becomes progressively more pronounced when the strain of surgery is put upon it. He believes that the damaged liver cells, failing in their function, liberate into the circulation some toxic substance which produces damage to the renal epithelium. It is believed that Quick's hippuric acid test for the detoxifying function of the liver is of value in detecting the underlying dysfunction of the liver.

THE LIVER

ABSCESS OF THE LIVER

This may be due to infection (1) from the systemic circulation, (2) from the portal vein, and (3) from the bile duct.

In tropical countries the so-called *solitary abscess* complicating amebic dysentery is a common condition. Although the abscess may be single there are quite frequently several present. The common site is the upper part of the right lobe, producing upward displacement of the dome of the

diaphragm on that side. The contents are viscid and chocolate colored, but usually inoffensive. The abscess may rupture into the peritoneal cavity or into the lung. In some cases the pus becomes absorbed.

Multiple abscesses may be pyemic, pylephlebitic, or cholangitic.

1. **Pyemic Abscesses.**—In any pyemic condition small abscesses may be found scattered throughout the liver, the result of septic emboli (Fig. 224). The condition is terminal and not of any surgical importance.

2. **Pylephlebitic Abscesses.**—Suppurative pylephlebitis or thrombophlebitis of the portal vein is usually due to acute appendicitis but may be caused by suppuration in the pelvis, in inflamed hemorrhoids, etc. The

Fig. 224.—Multiple abscesses of the liver occurring in a general pyemia.

greater part of the vein may be affected by thrombosis and inflammation, infected emboli are carried to the liver, and a condition of *portal pyemia* results, with the formation of multiple small abscesses scattered through the liver, which is enlarged and tender (Fig. 225). In spite of the frequency of acute appendicitis, this complication is rare, because the thrombosis is in advance of the inflammation and it seals up the vessels.

3. **Cholangitic Abscesses.**—These abscesses are secondary to cholangitis, usually due to a stone in the common bile duct. The abscesses follow the distribution of the bile ducts in the liver. There is enlargement of the liver, and the abscesses, which contain bile-stained pus, may be much

Fig. 225.—Abscess of liver. Portal infection from appendix.

Fig. 226.—Cholangitic abscesses of the liver.

larger than in the two previous forms (Fig. 226). The patient is jaundiced and develops the intermittent temperature known as Charcot's intermittent hepatic fever.
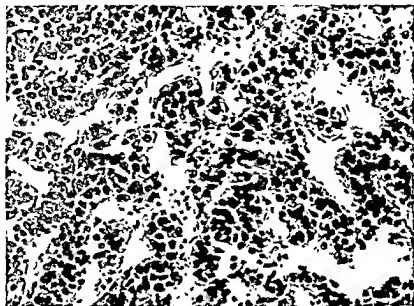
Fig. 227.—Primary liver cell carcinoma. × 200.

Fig. 228.—Primary bile duct carcinoma of liver. × 175.

TUMORS

Primary Carcinoma.—This is a rare disease, and the diagnosis should only be made at autopsy when every possibility of secondary growth has been excluded. In one of our autopsy cases no primary tumor could be found, but it was noticed that the patient had a glass eye; the tumor in

the liver was a secondary melanoma. Although the condition is so rare in the white man, it is very common in the Chinese, in whom cirrhosis of the liver is also common. The cancer may arise from liver cells (hepatoma) or bile ducts (cholangioma). The *hepatoma* or liver cell cancer is the commoner type. The tumor may be massive, or may take the form of multiple small nodules scattered through the liver. Both forms are very commonly associated with well marked portal cirrhosis. It is probable that the cirrhosis is the primary condition, the carcinoma arising in the nodules of regenerative hyperplasia. The patient occasionally has symptoms of cirrhosis long before the development of carcinoma. Microscopically the tumor cells are arranged in interlacing columns or quite irregularly (Fig. 227). Multinucleated giant cells are common, and may attain a great size. Metastases in other organs are comparatively rare. Fever is frequent, especially when there is much necrosis. The *cholangioma* or bile duct carcinoma is rarer and is not often associated with cirrhosis. It is multiple in form. Microscopically it is adenocarcinomatous in type (Fig. 228), but the distinction between liver cell carcinoma and bile duct carcinoma is sometimes very difficult.

Fig. 229.—Secondary carcinoma of the liver.

Secondary Carcinoma.—The liver is one of the commonest organs to show metastatic growths. Any part of the gastrointestinal canal, draining as it does into the portal vein, may be the seat of the primary tumor. Of these the stomach is the most frequent. Less commonly the primary growth may be in the kidney, adrenal, uterus, breast, or lung. Malignant melanoma, often primary in the eye, may metastasize to the liver.

The tumors are multiple, and are situated rather towards the surface than at the center (Fig. 229). They are often soft and necrotic, and in color may be yellow from necrosis or green from bile staining. An excellent color illustration of the condition will be found in Karsner's textbook. Owing to the necrosis in the superficial tumors, there is often a falling in of the central part of the surface, the so-called umbilication. The cirrhosis so constantly seen in primary carcinoma of the liver is not found in the secondary growths.

Willis points out that invasion of the larger portal tributaries in the

liver by tumor growth is responsible for the multiplicity of nodules, even though there is only a single metastasis in the first place. Invasion of efferent veins is responsible for further dissemination to the lungs.

Cavernous Hemangioma.—This tumor is not uncommonly found in the autopsy room. It gives rise to no symptoms. Forming a small red or purple mass on the surface, from a few millimeters to several centimeters in diameter, it is apt to be mistaken for an infarct. Microscopically it presents the usual appearance of an angioma, consisting of large cavernous blood-filled spaces.

HYDATID CYSTS

The liver is the organ most frequently affected by the hydatid cysts of echinococcus disease. The Taenia echinococcus is by far the smallest of the tapeworms, measuring only half a centimeter in length. It consists of a head and neck and three or four segments. It lives in the intestine of the dog, and the embryos, passed in the feces, may be ingested by man in contaminated food. The embryos bore through the wall of the intestine, and are carried to the liver, and it may be to any other part of the body. In the liver the embryo settles down and develops into a larval or cysticercus stage. The fully-formed cyst wall is composed of concentric laminae, so distinctive that the structure can readily be recognized microscopically, and is lined by a germinal layer from the cells of which grow daughter cysts, and within these again grand-daughter cysts. Within these cysts great numbers of new individuals are formed, or rather the scolices or heads from which these individuals will be formed when they again gain access to the intestine of the dog. Each scolex is armed with a row of small hooklets, and the finding of these hooklets, which persist for many years, is of great diagnostic value. The watery contents of the cysts apparently have antigenic powers, for they may be used as an antigen in the complement fixation or precipitin tests for the disease. Escape of the fluid from rupture of a cyst may give rise to marked urticaria, and the fluid may be inoculated into the skin after the manner of the skin tests for protein hypersensitiveness.

If man were the only intermediate host the disease would soon die out, but other animals such as the pig and sheep may perform this office, and when their organs containing the hydatid cysts are devoured by dogs, the life cycle of the worm is completed. As a matter of fact the disease is seldom seen nowadays except in those countries where man comes in very close contact with his dogs, as in Iceland, or in great sheep-raising countries, such as Australia. Even in Iceland the incidence of the disease has greatly decreased in recent years.

The condition of the liver naturally varies greatly, depending on the size and position of the cysts. It may be considerably enlarged, and the mass which is often felt on the anterior surface may readily be mistaken for a tumor. The larvae die out in the cysts after a number of years, and the contents then tend to become inspissated and converted into a putty-like mass. In other cases the cyst may rupture into the abdominal or pleural cavities, or into one of the neighboring hollow viscera. The most unfortunate sequel is the occurrence of infection, with the conversion of the cyst into an abscess, the clinical picture changing to one of pyemia.

Non-parasitic Cysts.—Other cysts which may occur in the liver are lymphatic cysts, bile duct retention cysts, and cystic degeneration of the liver and kidneys (congenital cystic kidney). All of these are congenital. The lymphatic cysts may attain a considerable size.

GUMMA

The only form of syphilis of the liver which is of surgical importance is the gumma. The lesions are more often multiple than single, and are

Fig. 230.—Two gummata of the liver.

Fig. 231.—Hepar lobatum.

usually in the right lobe. They may be several centimeters in diameter and have an elastic or a necrotic character (Fig. 230). The surgical importance of the gumma lies in the fact that it may be confused with

other conditions. The multiple lesions may simulate secondary carcinomata. When healing occurs very deep scars are formed, and these may divide off one or more large nodules of liver tissue which may be mistaken for a simple tumor (hepar lobatum) (Fig. 231). A surgeon with more operative zeal than pathological knowledge has been known to remove one of these masses of normal liver tissue.

ACTINOMYCOSIS

This rare condition is secondary to actinomycosis of the intestine. The liver is enlarged, and the cut surface of the affected area presents a honeycombed appearance, as of a sponge dipped in pus. The pus contains the usual "sulphur granules." The abscess may rupture through the diaphragm into the lung, into the stomach, or on the abdominal wall.

OBSTRUCTION OF THE COMMON BILE DUCT

The cause of the obstruction may be (1) outside the duct (pressure of a carcinoma of the head of the pancreas, malignant glands, etc.), (2) in the wall of the duct (simple stricture due to post-inflammatory fibrosis), (3) in the lumen (gall stone impacted in duct, tumor). The effects depend on the completeness and rapidity of the obstruction, and even more on the presence of pre-existing inflammation causing fibrous thickening of the ducts and gall bladder. The effect of the obstruction is threefold: (1) hydrohepatosis, (2) the formation of "white bile," (3) obstructive jaundice.

1. **Hydrohepatosis.**—Obstruction to the escape of bile from the liver produces an effect not only on the common duct, the hepatic duct, the cystic duct, and the gall bladder, but upon the whole biliary tree within the liver. Counseller and McIndoe have shown by means of celloidin injections of the bile ducts followed by corrosion that the entire biliary tree may become dilated to a degree hitherto undreamt of. This condition is known as hydrohepatosis. Malignant occlusion occurring in an uninfected duct produces severe hydrohepatosis with little or no fibrous thickening; the gall bladder is dilated and thin-walled. If the obstruction is due to a stone in the common duct there is likely to be only slight or moderate dilatation of the ducts fibrosed and thickened by cholangitis; the gall bladder is thick-walled and contracted (Courvoisier's law). The dilatation of the ducts within the liver exerts serious effects on the liver cells.

2. **"White Bile" Formation.**—Bile is normally secreted by the cells of the liver into the bile ducts. When the back pressure from the obstruction becomes sufficiently great (300 mm. of water), the secretion stops, no more bile is produced, and the bile already in the biliary passages is absorbed. The mucous glands in the walls of the ducts continue to secrete in spite of the pressure, and presently the biliary passages become filled with clear watery fluid containing a trace of mucin. This is known as "white bile," but it contains none of the constituents of bile. When the obstruction is relieved it may be some time before the liver cells commence to produce normal bile again. If the gall bladder is healthy the onset of the above described condition is delayed, because the normal absorption of bile from the gall bladder relieves the pressure on the liver cells. When

the gall bladder is diseased the replacement of normal bile by "white bile" is much more rapid, and may occur in a week after complete obstruction.

3. Obstructive Jaundice.—The bilirubin of the bile is formed from blood pigment by the Kupffer cells of the liver and by other members of the reticulo-endothelial system throughout the body. The pigment thus formed is excreted by the hepatic cells into the bile ducts. If it cannot pass into the duodenum it is reabsorbed into the blood stream, where it gives a positive *direct* van den Bergh reaction, in distinction to hemolytic jaundice where the reaction is *indirect*. The bilirubin collects in the blood, tinges all the tissues of the body including the skin and the whites of the eyes, and is excreted in the urine. In long-continued obstructive jaundice there may be marked *impairment of liver function*, due mainly to the pressure of the dilated bile canaliculi on the hepatic cells, although the action of retained toxins may play some part. The patient may die in a toxic state of *cholemia*, with symptoms like those of uremia. At autopsy the effects of the toxins are seen throughout the body, but especially in the convoluted tubules of the kidney. The *coagulation time* of the blood is much increased, so that there may be continued oozing of blood after operation when the jaundice is marked. Slow intra-abdominal hemorrhage is a common cause of death in patients with obstructive jaundice who have been operated upon. The hemorrhage is a manifestation of vitamin K deficiency. There is sufficient vitamin K (coagulation or antihemorrhagic vitamin) in the food, but it is not absorbed from the bowel unless bile is present. In obstructive jaundice bile is naturally not present. Owing to lack of absorption of vitamin K, prothrombin is not formed by the liver in the required amount, so that the blood level of prothrombin is below normal. As the formation of thrombin (clotting of blood) is dependent on an adequate prothrombin level, the clotting power in obstructive jaundice will be impaired, and hemorrhage from minute vessels after operation may be expected. By determining the prothrombin level a deficiency in vitamin K can be detected, and this can be remedied before operation by administering the vitamin combined with bile, or by giving the synthetic vitamin intravenously or intramuscularly.

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THE PANCREAS

ACUTE HEMORRHAGIC PANCREATITIS

This condition is better called acute pancreatic necrosis, for there may be no hemorrhage, and the lesion is more necrotic than inflammatory. The old name, however, is hard to dislodge.

The *clinical picture*, first described by Fitz of Boston in 1889, has been drawn with great vividness by Lord Moynihan. As he remarks, the suddenness of its onset, the illimitable agony which accompanies it, and the mortality attendant upon it, all render it the most formidable of catastrophes. The pain, more terrible even than that of the perforation of a gastric or duodenal ulcer, is remarkable in that it comes so frequently after a good meal. The patient with hepatic or renal colic changes his position every minute, seeking the relief which does not come. The patient with acute pancreatic necrosis, like the one with a perforated ulcer, remains motionless. There is a degree of shock which is never present in other conditions. The face sometimes presents a peculiar cyanosis which is never seen in other acute abdominal conditions, and there may be patches of a slate-blue color on the surface of the abdomen.

Etiology.—The necrosis is due to the action of pancreatic enzymes liberated from the ducts. But how these come to be liberated is still undecided. It is commonly believed that the trypsinogen of the pancreas must be activated and converted into trypsin by intestinal juice or infected bile before it can digest tissue. The original view was that of Opie, to the effect that there was mechanical obstruction of the ampulla of Vater either by an impacted gall stone or by a plug of mucus. In those cases where the pancreatic duct joins the bile duct a short distance from the common opening into the duodenum, such an obstruction would cause bile from above to pass into the pancreas. In isolated cases this may be the correct *explanation, but it is quite exceptional to find an impacted stone, and it* is probable, as Archibald has shown experimentally, that spasm of the sphincteric muscle of Oddi at the outlet of the common duct is the usual cause of the obstruction. Archibald found that when spasm of the sphincter was produced in cats, as could be done by pressing on the gall bladder or painting the ampulla with weak acid, bile passed into the pancreas, and if this bile was heavily infected the animal would die in the course of a few hours with acute hemorrhagic pancreatitis. Mann and Giordano have rather spoiled this satisfying theory by pointing out that the sphincter in man is not placed distal to the entrance of both ducts in the ampulla, but is usually proximal to the termination of the bile duct. It may be, as these authors remark, that clinical imagination has preceded demonstrated facts.

Rich and Duff have suggested a quite different approach to the prob-

lem. They found that pancreatic juice was able to produce necrosis without activation of the trypsinogen by intestinal contents or bile, and believe that the mechanism of escape of pancreatic secretion is rupture of thinned-out acini behind an obstructed duct. Such rupture is precipitated by increased pressure in the ducts caused by marked secretion after a large meal. The main duct may be obstructed by a gall stone at the ampulla or by spasm of the sphincter, but in most cases the obstruction seemed to be in one of the smaller ducts, due, they believe, to metaplasia and heaping up of the lining epithelium. This lesion was present in over half the cases of hemorrhagic pancreatitis. The lesion is found in cases where there is no pancreatitis, but this fact does not invalidate the theory. The probable truth is that all of the factors outlined above may at times be responsible for producing acute pancreatitis. Whatever be the mechanism by which the enzyme escapes from the ducts, the walls of the vessels are digested and undergo necrosis, and this is responsible for the hemorrhage.

The *cause of death* appears to be an overwhelming of the patient by the poisonous split-protein products formed as the result of partial digestion of the pancreatic tissue. The wholesale absorption of these intensely poisonous substances accounts for the extraordinarily rapid termination of many of the cases. It is the same mechanism which has been shown by Whipple to be responsible for the intoxication in high intestinal obstruction.

Morbid Anatomy.—The naked-eye changes are usually striking and spectacular. It must be remembered, however, that acute necrosis may exist in a pancreas which is apparently normal. The varieties originally described by Fitz as hemorrhagic, gangrenous, and suppurative are merely subdivisions of the one process. The pancreas is usually enlarged, sometimes to two or three times the normal size, of varying consistence—hard in the milder forms, very soft and friable in the more severe types—and the surface may show opaque whitish areas of fat necrosis, extensive areas of hemorrhage, or it may be black and gangrenous. The changes may be confined to the head, or may involve the entire organ. In many cases there is no hemorrhage. In others the hemorrhage dominates the picture. *Microscopically* there is profound necrosis of the pancreatic tissue, so that in the advanced cases no normal structure can be made out.

The result depends on the extent of the necrosis. If only small areas are involved they may be absorbed and replaced by fibrous tissue. Larger areas break down, become infected with bacteria, and give rise to abscess formation. The greater part of the pancreas may slough away.

A very characteristic feature is the presence of a sanguineous or serosanguineous exudate in the lesser sac of peritoneum. This exudate contains pancreatic ferments, and is as a rule sterile. It has been shown to exert a protective influence, so that it cannot be removed with impunity. Later, however, it may become infected and give rise to an acute peritonitis.

Fat Necrosis.—Perhaps the best known phenomenon of acute pancreatic necrosis is the occurrence of the peculiar white spots known as fat necrosis (Fig. 232). These areas are of a dull, opaque, whitish appearance, contrasting strongly with the yellow glistening fat by which they

are surrounded. They are most abundant in the vicinity of the pancreas, but may be scattered far and wide over the mesentery and the omentum. The subperitoneal fat of the abdominal wall may be involved, and the

Fig. 232.—Acute hemorrhagic pancreatitis. Numerous areas of fat necrosis are scattered over the fat on the surface of the pancreas.

change has even been found in the pericardium and the mediastinum. *Microscopically* the necrosed fat cells have a characteristically opaque appearance (Fig. 233). One part of a fat globule may be opaque while the other part is clear. The necrotic area is surrounded by a ring of leucocytes.

That these areas are directly due to the action of the fat-splitting ferment of the pancreas has been proved by the discovery within them by Flexner of the pancreatic lipase. The neutral fat is broken down into glycerine and fatty acids, and the latter soon combine with calcium to form an insoluble soap. The areas tend to be *absorbed in the course* of a few weeks.

If the fat necrosis is due to the liber-ation of the pancreatic ferment it may be asked why the necrotic areas should be discrete and patchy. The answer is that the digestive fluid cannot have flowed over the surface of the fat, otherwise the change would be a diffuse one. Moreover the epithelium covering the affected patches is quite intact. The lipase must have been carried by the lymph or possibly by the blood channels, picking out here and there an area for attack.

Fig. 233.—Fat necrosis. × 450.

Fat necrosis always indicates a coexisting pancreatic necrosis, although in some cases the pancreas is to all appearances normal. In an autopsy on

a case of carcinoma of the cervix uteri numerous areas of fat necrosis were found around the pancreas, although that organ was of the usual size and consistency. Microscopic examination, however, showed typical areas of pancreatic necrosis.

PANCREATIC CYSTS

Cysts of the pancreas, although far from common, are not so rare as used to be supposed. They may be divided into three groups: (1) cystadenomata, (2) retention cysts, and (3) pseudocysts. Of these the last are by far the most important.

Cystadenoma.—These are true tumors. The tumor is often multilocular, spaces are lined with high epithelium, and papillary processes may project from the walls.

Retention Cysts.—These are small cysts, the origin of which is somewhat uncertain. Ligature of the pancreatic duct is not accompanied by cyst formation, but it may be that intermittent or partial obstruction may result in dilatation of the duct, as in the case of the ureter. Chronic interstitial pancreatitis is often associated with the cyst formation, but it may well be a result rather than the cause of the condition.

Pseudocysts.—Most of what are called cysts of the pancreas are not cysts at all, but pseudocysts. They may attain a considerable size, and may be mistaken for echinococcus cysts, ovarian cysts, hydronephrosis, or a perinephritic abscess. They are not situated in the substance of the pancreas but in the immediate neighborhood, usually in the lesser sac of peritoneum which lies immediately in front of the pancreas. In this group may also be included the degenerative cysts which develop in superficial portions of the pancreas which have broken down as the result of acute pancreatic necrosis.

The chief causes of pseudocysts are a previous attack of acute necrosis and injury to the pancreas from trauma. As the result of a superficial lesion there is an escape of pancreatic secretion or inflammatory exudate into the lesser sac, the foramen of Winslow becomes sealed, and a cyst develops.

The contents vary considerably in their gross appearance. They may be clear and serous, yellow, brown, or black, depending largely on the amount of blood they contain. The chief constituents are inflammatory exudate, liquefied necrotic pancreatic tissue, and altered blood. In one of Archibald's cases a reaction for bile was obtained.

Examination of the fluid as an aid to diagnosis is of little or no value. The presence of all three of the pancreatic ferments does not prove that the fluid is pancreatic in origin, for any cyst into which hemorrhage has occurred may contain these ferments. The presence of trypsin in large amount, however, is suggestive of a pancreatic origin. On the other hand many pancreatic cysts contain no ferment.

CARCINOMA OF THE PANCREAS

The only common tumor of the pancreas is carcinoma. Kaufmann found this condition present in 1.76 per cent of autopsies on malignant tumors. It is much commoner in men than in women.

In at least two-thirds of the cases the tumor occurs in the head of the

gland. The affected part is enlarged and as a rule extremely hard. The common bile duct is frequently surrounded by the growth with, as a result, a deep, persistent jaundice. The gall bladder is dilated in accordance with Courvoisier's law that obstruction within the duct, as by a stone, leads to a shrunken gall bladder with thick walls, whereas obstruction due to pressure from without results in a thin-walled dilated one (Fig. 234).

Even when the abdomen is opened and the hard mass in the head of the pancreas is in the hand of the surgeon, it may be difficult or impossible to be sure whether the condition is carcinoma or merely a chronic inflammatory thickening. Even the presence of enlarged nodes in the neighborhood is not certain proof of carcinoma, for such enlargement may also be

Fig. 234.—Extreme dilatation of the gall bladder and bile ducts due to cancer of the head of the pancreas.

the result of inflammation. Not infrequently the surgeon has the gratifying experience of closing the abdomen on an apparently hopeless carcinoma of the pancreas, only to find that the patient makes a complete and spontaneous recovery.

Secondary growths are common, and are first seen in the lymph nodes and the liver. Numerous minute nodules are often scattered throughout the liver, but without any enlargement of the organ, whereas growths secondary to gastric carcinoma cause bulky enlargement of the liver. Occasionally the metastases are more widespread. In one of our cases not only was the peritoneum covered with small, hard, button-like nodules, but both lungs were studded with similar growths. These, almost without exception, were situated immediately under the pleura, to which indeed they were attached. The spread was apparently through lymphatic

channels. Distant dissemination through the blood stream is of rare occurrence.

Microscopically the tumor may be either an adenocarcinoma or scirrhous in type. It may arise from the ducts or the acini. The duct tumors are much commoner; the cells are columnar or cuboidal, with clear-cut outlines, vesicular nuclei, and distinct nucleoli. The acinar tumors are rare; the cells are polygonal or rounded, their outlines indistinct, with large hyperchromatic nuclei and inconspicuous or absent nucleoli.

Cancer of the body and tail does not produce jaundice, but it differs also in other respects from cancer of the head of the pancreas (Duff). Spread is a much more striking feature. Deep-seated gnawing pain is a characteristic feature due to extensive involvement of perineural lymph spaces, as the tumor is likely to be in direct contact with the celiac plexus. Ascites is common, and is usually due to implantation growths on the peritoneum or involvement of the portal vein. The spleen may be enlarged owing to pressure on the splenic vein which lies in a groove in the body of the pancreas. Distant metastases both by the blood and lymph stream are commoner than in cancer of the head.

Secondary carcinoma is usually due to direct invasion. Of all the organs in the abdomen the pancreas is the one most liable to direct invasion. On two occasions I have seen the entire pancreas diffusely replaced by the spread of a hypernephroma.

Tumors of the Islets of Langerhans.—It is now possible not only to diagnose but also to remove a tumor of the islets of Langerhans. The tumor is usually circumscribed and benign, an adenoma of the islet tissue, as can be

Fig. 235.—Islet cell tumor. × 150.

proved by recovering insulin from the specimen or by demonstrating the presence of the specific granules of islet cells. As a rule it is quite small. Sometimes there is a general hyperplasia of islet tissue throughout the pancreas, and in rare cases carcinoma of the islets is said to occur. *Microscopically* the tumor usually duplicates the pattern of normal islets (Fig. 235), as may be seen in the illustrations to Laidlaw's paper. It is indeed a gigantic islet. It may exaggerate some features of the normal pattern; thus the cells may be arranged in the form of ribbons. A simple way to distinguish between tumor cells and the cells of the gland acini is to stain the zymogen granules of the latter; this is much easier than to stain the specific granules of the tumor (islet) cells. The tumor produces an excess of insulin, so that the patient manifests symptoms of hyperinsulinism, *i. e.*, attacks of faintness and unconsciousness coming on as a result of fasting, attacks which are at once relieved by taking glucose. The hypoglycemia which is the basis of the symptoms is completely relieved by removal of the tumor.

ABERRANT PANCREATIC TISSUE

It sometimes happens that portions of normal pancreatic tissue are found in the wall of the duodenum or stomach, more rarely in other parts of the bowel, and even under the capsule of the spleen. These vary in size from the most minute up to 3 or 4 inches in diameter. They usually contain islets of Langerhans as well as the ordinary acinar tissue. The condition is merely the persistence in man of a state of affairs normally present in some of the lower animals. In certain amphibia, for example, portions of the pancreas are regularly found in the wall of the stomach and duodenum. As Warthin suggests, developing buds of pancreatic tissue are probably snared off by the surrounding mesoderm and separated from the main organ.

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THE PERITONEUM

Anatomical and Physiological Considerations.—The peritoneum is a serous membrane lining the abdominal wall and providing a covering to the abdominal viscera. The peritoneal cavity is, in health, merely a potential cavity, and contains only a few drops of serous fluid. In the male it forms a completely closed sac, in the female the Fallopian tube communicates with it by a minute opening, a point of great importance, as by this means a uterine infection may reach the peritoneal sac. The various folds and fossae of the peritoneum are of great surgical importance, but this is not the place in which to discuss them.

The peritoneum consists of a layer of flattened epithelial cells supported by a small amount of subepithelial connective tissue. Outside there is the subperitoneal connective tissue, which in some places contains a large amount of fat.

The normal peritoneal fluid contains about 2300 cells per c.mm. (Dixon and Rixford). The majority of these are histiocytes (mononuclears); there are many lymphocytes, and a few polymorphonuclears and eosinophils. The intraperitoneal injection of foreign material in laboratory animals produces a great increase in the number of polymorphonuclears, which are replaced by mononuclears in the course of a few days. It appears probable that at least part of the protection afforded by intraperitoneal inoculation is the result of non-specific phagocytosis due to increase in the number of histiocytes, which are more phagocytic than the polymorphonuclears.

Valuable information may be obtained as to intra-abdominal conditions from a cytological examination of peritoneal fluid obtained either by abdominal puncture or at the outset of an abdominal operation as soon as the peritoneum is incised. A report on the smear can be obtained in the course of five or ten minutes. Abdominal puncture will determine whether postoperative intestinal distension is due to peritoneal infection or merely the result of atony of the bowel; in the former case from 85 to 95 per cent of the cells will be polymorphonuclears, whilst in the latter there will be a predominance of mononuclear cells. For details of the procedure the reader is referred to papers by Steinberg.

The peritoneal sac is a closed sac, apart from the openings of the Fallopian tubes in the female. It used to be regarded as a great lymph space in communication with the lymphatic system, but we now know that that system is itself a closed space, and that there exists no direct communication between the two.

The presence of the *stomata* between the epithelial cells which used to be described in silver nitrate preparations was taken as an indication of ready absorption from the peritoneal sac into the lymphatic system. It is now known that these stomata have no real existence, but are merely

spurious products formed by a precipitate of silver. Indeed they may be produced independently of a serous membrane, for, when silver nitrate and a dilute solution of albumin are mixed and allowed to evaporate on a slide, an appearance is seen identical with that of the so-called stomata. For a full discussion of this and other histological questions the reader is referred to Hertzler's 800-page monograph on the peritoneum.

Although there is no direct communication by means of stomata between the peritoneal sac and the lymphatic system, absorption occurs very readily. Not only colored fluids but small particles may be removed from the peritoneum in this way. It is generally considered that absorption is largely confined to the upper part of the abdominal cavity, and especially to the diaphragmatic surface. This assumption has led to the adoption of the Fowler position in the treatment of acute diffuse peritonitis. The patient is placed in a sitting position so that the purulent material may collect in the pelvis rather than in the upper abdomen and thus avoid being absorbed.

The basis for this view of peritoneal absorption is the fact that the lymphatics of the diaphragm are so much more easily demonstrated than those of other peritoneal surfaces, and especially the abundance in that position of the fictitious stomata. It is now known, however, that absorption takes place readily from all parts of the peritoneal surface. Dandy and Rowntree have shown that in whichever part of the peritoneal sac toxic substances are placed, the rate and degree of absorption are the same. On theoretical grounds there is no justification for the Fowler position, although empirical observations may have another tale to tell.

The rate of absorption is usually supposed to be hastened by the presence of inflammation. There again exact experimental observations are against the popular view. When phenolphthalein or methylene blue is introduced into the abdominal cavity in the course of a laparotomy, it will be found that the time at which the dye appears in the urine depends upon the nature of the inflammatory exudate; in every case of inflammation absorption is found to be delayed, and when the exudate is very fibrinous and abundant there is practically no absorption.

Although there is no direct communication between the peritoneal and pleural cavities, yet septic and other material may pass indirectly from one to the other. The peritoneal surface of the diaphragm is studded with minute pits into which the membrane dips, and which come into close relationship with the lymphatic plexus of the diaphragm. Occasionally, though by no means frequently, bacteria may succeed in entering these lymphatics, whence they are carried to the mediastinal glands, and in this way the pleura may be secondarily infected. Wilkie has pointed out recently how frequently acute inflammation of the gall bladder is associated with signs of infection (moist râles) at the base of the right lung.

The *omentum* is a specialized portion of the peritoneum which deserves separate mention. Various theories have been suggested as to its function in health, such as protection, fat storage, etc. It has marked absorptive powers, and plays an important part in the removal of bacteria and foreign substances. Indeed it has been shown that when bacteria are injected intraperitoneally in not too large quantities, none may be found in the peritoneal fluid at the time of death, and yet abundant

cultures may be obtained from the omentum. This explains in part the frequent sterility of a peritoneal exudate, even when the condition proves fatal.

Rutherford Morison, in his Introduction to Surgery, has some excellent remarks on the functions of that abdominal policeman, the omentum, from which the following is taken. "It travels about in the abdomen with considerable activity, and is attracted, by some sort of information, to neighborhoods in which mischief is brewing. It may effect a radical cure of hernia, by blocking the hernial orifice with an omental plug. It sur-
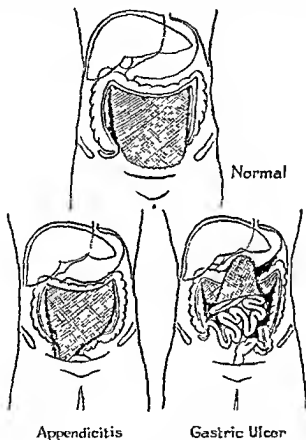
Fig. 236.—To illustrate the protective function of the omentum. (After Rutherford Morison.)

rounds, and adheres to, a recently reduced strangulated and damaged loop of intestine; and may keep it alive and prevent a leak. It is generally found in the neighborhood of a diseased or inflamed appendix; by wrapping it up if gangrenous, or by blocking up the pus from an appendical abscess, it may prevent general peritonitis. In a similar manner it may prevent the perforation of an ulcerating malignant growth, of a gastric ulcer, or the death of a damaged portion of bowel, or the perforation of a suppurating gall bladder. When it is found covering and closely enveloping an ovarian cyst or a fibroid tumor of the uterus, even though not adherent,

it is safe to assume that something wrong will be found in the tumor. Its effective mobility is shown by the fact that whether the lesion be in the diaphragmatic roof of the abdomen or on the floor of the pelvis, there the omentum can and does find its way" (Fig. 236).

The important diseases affecting the peritoneum are acute and chronic inflammation, tuberculosis and malignant disease; other rarer conditions are hydatid cysts and actinomycosis.

ACUTE DIFFUSE PERITONITIS

The cause of acute peritonitis is that of inflammation elsewhere, namely the presence of an irritant. In the vast majority of cases this irritant is bacterial in nature. Passing consideration may, however, be given to *non-bacterial irritants*.

The presence of a foreign body such as a strip of gauze or a drainage tube will give rise to a peritonitis, which usually remains localized. An effusion of blood, such as that from a ruptured tubal pregnancy, will act in a similar manner. So will the escape of fluid from a cyst, a dilated gall bladder, etc.

Even in these cases, however, it is doubtful if we are dealing with a strictly aseptic peritonitis. Dudgeon and Sargent have shown that in these cases, and especially in hemorrhagic effusions, Staphylococcus albus can usually be demonstrated. Its presence appears to be beneficial rather than injurious, for it provides the stimulus necessary for the accumulation of phagocytes without giving rise to a progressive inflammation.

Of the *bacterial irritants* the commonest is Bacillus coli, with the streptococcus a good second. Less frequent are the staphylococcus, the pneumococcus, the gonococcus, Bacillus pyocyaneus, the typhoid bacillus, and certain anaërobic bacilli. The infection is frequently not pure but mixed.

Infection may reach the peritoneal cavity in three ways:

(1) From the exterior by an accidental wound, or it may be in the course of an operation. Those cases in which the infection, puerperal, pneumococcal or gonococcal, passes along the Fallopian tube to the peritoneal cavity are included in this group.

(2) From the alimentary canal, one of its derivatives such as the pancreas or gall bladder, or an adjacent organ such as the kidney. Most cases are secondary to appendicitis. If the appendix is perforated the peritonitis is severe and stormy; if not perforated the disease is usually mild, even if the appendix is gangrenous. Perforation of the gall bladder is always fatal, due to the irritation produced by bile.

(3) From the blood stream. This, by far the rarest method, is seen in one type of pneumococcal peritonitis.

The prognosis of the disease varies greatly, depending on three factors: (1) the virulence of the bacteria, (2) the resistance of the patient, and (3) the source of the infection. Regarding the first it may be said that the streptococcus is the most virulent of the invaders, the Bacillus coli may be relatively harmless or on the other hand may be quite virulent, and the pneumococcus usually produces a fatal infection. The second is an imponderable quantity. The source of infection is an important factor.

Peritonitis secondary to ruptured duodenal ulcer or ruptured typhoid ulcer runs a rapid and fatal course. Speaking generally, infections in the upper part of the abdomen are more likely to end fatally than those in the lower part. Smears made at operation are of prognostic value; if no bacteria are found the outlook is good. If the culture is negative the peritonitis is generally limited to the focus of infection; if growth is present the peritonitis is generally diffuse. Meleney points out that there is a steady increase in the severity of the disease corresponding to an increase in the number of species present. Peritonitis is generally a polymicrobic disease.

Peritonitis commences locally. It may remain local, or may spread and become diffuse. At first the peritoneum simply looks pinker and more

Fig. 237.—Acute peritonitis. Coils of bowel intensely congested and covered with a fibrinous exudate represented by white streaks.

injected than normal. Then the normal sheen is lost, owing to the deposition of a thin layer of fibrin on the surface (Fig. 237), which acquires a frosted or ground-glass appearance. The affected part becomes sticky, and the coils of bowel are gummed together.

Microscopic examination shows the usual appearance of an inflamed membrane. The epithelial cells are at first intact, but later may become desquamated. The exudate consists mainly of fibrin threads, with a variable number of leucocytes and it may be some red blood cells. As the disease advances both the exudate on the intestinal wall and the fluid exudate become entirely purulent.

At this stage one of three things may occur. (1) The disease may end by resolution. (2) Adhesions may be formed which keep the inflammation

strictly limited. (3) The infection may spread diffusely. These are the three fundamental possibilities of the inflammatory process already considered in Chapter II, namely, resolution, repair with fibrosis, and suppuration with tissue death.

The amount of fibrin deposited depends somewhat upon the infecting organism. In B. coli cases a thick matting is often deposited on the coils of bowel, binding them together in a naturally defensive reaction. In streptococcal cases, on the other hand, fibrin is often very scanty, with little or no matting; this, however, is by no means an invariable rule. During an operation no attempt should be made to strip flakes of fibrin from off the bowel, for the *phenomena of peritonitis are essentially protective*. The fibrin forms a protective covering, limits the spread of the disease, and when it is removed a raw surface is left from which septic absorption may readily occur. For the same reason only the gentlest manipulations are allowable.

In the meantime a fluid exudate is collecting. During the earliest stages this exudate is serous, but it soon becomes cloudy and more or less purulent, owing to the admixture of leucocytes and bacteria. The degree of purulence is an index of the resisting powers of the patient rather than of the virulence of the infection. The abdomen may be bathed in thick, creamy pus with little constitutional disturbance. A thin, more or less serous, and possibly blood-stained exudate with only an occasional floating flake of fibrin is very suggestive of a streptococcal infection associated *with low powers of resistance and a very bad prognosis*. The exudate may be purulent at the site of origin of the infection, but still serous at some distance away. Occasionally there may be a hemorrhagic effusion, due usually to such conditions as twists, strangulation, and thrombosis, in which there is great circulatory disturbance.

If the infection begins to spread, two main channels will be followed. (1) The bacteria may be spread over the surface of the peritoneum by the movement of the bowel. This is prevented to some extent by the protective, policeman-like behavior of the omentum, and by the numerous adhesions which are usually set up. (2) They may spread rapidly and extensively along the lymphatics in the subperitoneal connective tissue, much as erysipelas spreads along the lymphatics of the skin. This method is best seen in streptococcal peritonitis, where the infection may spread like wildfire.

Thrombosis of the mesenteric veins and those in the wall of the bowel is apt to occur when the inflammation reaches them. One result is the possible development of gangrene in a part of the bowel. Another is the ready passage outwards of the bacterial flora of the bowel, producing a mixed infection and great aggravation of the condition. Even comparatively mild degrees of inflammation may render the intestinal wall permeable to the bacteria in the gut.

Sampson Handley has emphasized the great importance of paralytic ileus as a complication of general peritonitis. A coil of small intestine lying in a pool of pus in the pelvis becomes paralyzed, and the resulting obstruction may be complete. According to Handley, death is only rarely due to septicemia; in the great majority of cases it is due to intestinal obstruction. The infection in the ordinary case of acute appendicitis begins in the pelvis and spreads upwards. In pelvic peritonitis the bowel is com-

monly paralyzed at two points: (1) the pelvic coils of ileum, (2) the pelvic colon. The importance of relieving the obstruction by surgical means at once becomes evident. The part which obstruction plays in acute peritonitis has been concisely expressed by Sir Cuthbert Wallace: "If the bowels can be made to act, the patient recovers; if they fail to act, he dies."

In cases which recover the removal of all traces of inflammation is as a rule remarkably complete. Not only are the fluid exudate and fresh fibrin absorbed, but even firm fibrous adhesions are dealt with in a surprisingly effective manner. An abdomen filled with adhesions may be found to be almost completely free if opened again at the end of a few months. Here and there, however, fibrous bands may be left as an evil legacy to plague the unfortunate one for many a day.

Although adhesions are usually dealt with in a wonderfully satisfactory manner by the peritoneum, there are cases in which a chronic adhesive peritonitis is the main pathological condition. No organisms may be discovered at any stage, but the condition must be due to some low-grade bacterial infection. At the same time there seems to be an element of personal idiosyncrasy, for in some patients the abdomen, for no apparent reason, will become filled with adhesions on an even grander scale each time that an attempt is made at their removal.

The general features of acute peritonitis having been described, a word or two may be devoted to the different bacteriological varieties.

Bacillus Coli Peritonitis.—This is the commonest variety. The organism is usually derived from the gastro-intestinal canal, owing either to perforation or to the outward passage of the germs through an inflamed bowel wall. The common source is an inflamed or perforated appendix. An inflamed gall bladder, pancreas, or other organ which may harbor the colon bacillus may be the starting point.

The exudate is abundant and purulent, more especially so in the neighborhood of the starting point of the infection. A large amount of fibrin is deposited on the peritoneum, and floats in the form of flakes in the fluid. A very characteristic fecal odor is noticeable when the chief seat of the trouble is approached. This odor, however, is not present in every case.

This variety of peritonitis is one of the less fatal and fulminating forms, especially when the infection is a pure one. Much more often than is suspected, however, the infection is mixed. An apparently pure culture of the luxuriantly growing colon bacillus is obtained, but the more delicate germs which are really doing the harm may be quite swamped. The earlier in the disease the culture is made, the more frequently will streptococci be found to be present. The culture should therefore be planted by the surgeon at the time the abdomen is opened, and cover-slip smears should always be made. Those cases which are due to perforation of the intestinal wall will of course always present a very mixed infection.

One variety of B. coli peritonitis deserves special mention, namely that which follows upon abdominal operation. It runs an unfavorable course, and is not benefited by reopening the abdomen. Moreover the symptoms so characteristic of peritonitis—fever, pain, and rigidity—are usually absent, yet the patient rapidly goes down hill.

Streptococcal Peritonitis.—Streptococcus pyogenes is the most viru-

lent although fortunately not the commonest of the causes of peritonitis. It may reach the abdominal cavity by any of the methods above mentioned, that is to say from the alimentary canal, from neighboring organs, especially the Fallopian tubes, from the exterior, or by the blood stream. Perhaps the two most important sources are puerperal sepsis and infection introduced from without.

The rapid spread of the disease, more particularly in the puerperal form in which the infection creeps along the tubes, is due to a subperitoneal cellulitis which may sweep the abdomen from end to end. Moreover the cells of the exudate appear to have none of the phagocytic power which they manifest in the B. coli form.

The exudate is thin and watery, only slightly purulent, lacking in odor, containing no flakes of fibrin. The deposit of fibrin on the peritoneal surface is comparatively slight, and the coils of bowel are not gummed together. This, no doubt, is another reason for the rapid spread of the infection. Cover-slip preparations show numerous chains of cocci.

Pneumococcal Peritonitis.—One of the most serious of the acute abdominal emergencies of childhood is pneumococcal peritonitis. It is true that it sometimes affects adults, but this is of such rare occurrence that the disease may be looked upon as one of childhood and youth.

The pneumococci might reach the peritoneum in three ways: (1) through the blood stream from some distant focus such as the middle ear; this is generally regarded as the only important route; (2) through the diaphragm from a pneumonia or empyema; (3) through the female genital tract, which is usually regarded as a very rare occurrence. The disease is at least three times as common in girls as in boys.

The disease may be divided into two main groups, primary and secondary. In the primary group the peritoneal inflammation is the original manifestation of the disease. In the secondary group the peritonitis is a development secondary to a previous pneumococcal infection elsewhere, such as a pneumonia or an empyema. No mystery surrounds the secondary form, and it is with the primary form alone that difference of opinion exists.

Primary pneumococcal peritonitis is much commoner in the female. Amongst 56 cases McCartney and Fraser did not find a single example in a boy. All the male cases were clearly secondary. Diarrhea, one of the most constant features of the primary form, is never seen in the secondary variety. The disease is almost confined to the poorer classes; other pneumococcal infections are not. Infection is not carried to the peritoneum by the blood stream. It is true that pneumococci are found in blood culture, but they have been absorbed from the peritoneum. The infection reaches the peritoneum from the genital tract through the Fallopian tubes. At operation the fimbriae were seen to be congested, and mucopurulent material could be expelled from the interior of the tubes. At autopsy the tubes showed catarrhal inflammation and pneumococci were found in every instance. Careful search for other foci of pneumococcal infection especially in the middle ear, gave negative results. The disease commences as a pelvic peritonitis; in the early cases laparotomy shows a much heavier infection in the lower than in the upper abdomen, and in one case pneumococci were found in the vagina and the pouch of Douglas but not else-

where, although they were present in the blood stream. An analysis of the age incidence shows that the great majority of cases occur between the third and seventh years, and in particular in the fifth and sixth years. In this connection there are two interesting points: (1) it is often only after the third year that epithelial separation of the walls of the vagina is fully established; (2) up to the period between the seventh and eighth years the vaginal secretion is alkaline, whilst after that period it becomes acid and presents a barrier against infection. The statistics of the Hospital for Sick Children, Toronto, provide an interesting contrast to those which have just been quoted. Of 39 cases of proved primary pneumococcal peritonitis, 30 were females and 9 were males. The mortality in the females was 53 per cent and in the males 77 per cent. In 19 cases of primary streptococcal peritonitis, 18 were females and only 1 was male. The average mortality was 73 per cent, but this was before the introduction of the sulphonamide drugs.

At operation the peritoneum is seen to be congested and plum-colored. In the early cases the only lesion found is a thin film of exudate over the pelvic viscera. After twenty-four hours the exudate becomes watery and contains flakes of fibrin. It is not until the fourth day that it becomes definitely purulent, for the virulence of the infection does not encourage an emigration of leucocytes.

We have considered streptococcal and pneumococcal peritonitis separately. Lipshutz and Lowenburg point out that in young children the two conditions may conveniently be considered together. They present the results of a study of cases of acute streptococcal or pneumococcal peritonitis in children under the age of six. The two conditions were indistinguishable without a bacteriological diagnosis. The mortality at this early age was 100 per cent. All the streptococcal cases were boys, and all but one of the pneumococcal cases were girls. The authors consider that the infection is hematogenous, being carried from a focus in the upper respiratory tract to the lymphoid tissue of the bowel in the region of the appendix.

Gonococcal Peritonitis.—This form occurs as a complication of gonorrhea. It is of course very much commoner in females both adult and children, but it may occur in males from infection of the seminal vesicles. In the female the infection is due either to a spread of the disease along the Fallopian tube and through the ostium, or to the rupture of a gonorrheal pyosalpinx.

The peritonitis which ensues is usually confined to the pelvis, although it may become general. Moreover, although acute for a short time, its characteristic manifestations are chronic in nature. A plastic exudate is formed which gives rise to very dense adhesions which bind the pelvic contents into a matted mass. "Violin-string" adhesions between the anterior surface of the liver and the diaphragm or anterior abdominal wall are often due to former gonorrheal salpingitis.

Peritonitis Due to Anaërobes.—Although the part played by anaërobic bacilli in the production of peritonitis is usually belittled, they may produce a fatal peritonitis. I once had the opportunity of observing a series of cases of anaërobic infection following operation on the intestinal tract in which the patient developed symptoms of shock a few days after the operation; the skin was moist and clammy, the pulse running and thready, the temperature moderately elevated, and the features drawn and anxious. The visceral peritoneum was injected, and the fluid exudate was watery and blood stained, but at autopsy there was very little local change. No aërobic organisms were present in these cases, but Bacillus welchii was found in smears and cultures both during life and at autopsy.

Autolytic Peritonitis.—When a piece of liver is excised and dropped into the peritoneal cavity, the animal will die of respiratory paralysis within twenty-four hours, the peritoneal cavity contains a fluid inflammatory exudate, and the excised piece of liver as well as the animal's liver are filled with gas bubbles and swarming with anaërobic bacilli. The same thing happens when one lobe of the liver is ligated, the animal dying much sooner than when the entire liver is removed. The transplanted piece of liver undergoes autolysis, with the *formation of toxic substances which apparently increase the permeability of the bowel* to Bacillus welchii and other anaërobic gas-forming bacilli.

Bile Peritonitis.—The presence of bile in the peritoneal cavity is frequently associated with peritonitis. If the bile is sterile the peritonitis is bland in type, the local and constitutional symptoms are mild, and the pool of bile becomes walled off. If the bile is infected the course is stormy and often rapidly fatal, and the peritonitis is widespread. In laboratory animals the experimental introduction of sterile bile into the peritoneal cavity is followed by a fulminating peritonitis, with anaërobic bacilli of the Welch type swarming in the fluid. This does not occur in man.

The escape of bile is usually due to injury or rupture of the biliary passages or of the liver. There is a peculiar group of cases in which bile escapes without any apparent rupture of the ducts. In this group there is acute or subacute *cholecystitis*, and bile seems to seep through the gall bladder wall. The peritoneal infection is severe, as the bile is heavily infected.

LOCALIZED PERITONITIS

Instead of being diffuse in its distribution the peritonitis may remain localized, so that a collection of pus is formed at and confined to one spot. This limitation is due to peritoneal adhesions, protective in character, which shut off a pocket from the general peritoneal sac. The anatomical folds and cul-de-sacs are naturally common sites for such collections.

The commonest variety is the periappendicular abscess which is walled off so securely that the infection can spread no further. Inflammation of the Fallopian tubes or of the gall bladder, or the presence of a gastric or duodenal ulcer may be associated with local purulent collections. The pus may eventually reach the surface and discharge there, or the abscess may burst into the general peritoneal cavity or into one of the hollow viscera. In old-standing cases the bacteria may die out and the pus become sterile. One of the most important forms, and one which demands separate consideration, is subphrenic abscess.

Subphrenic Abscess.—A collection of pus between the diaphragm and liver on the right side, the diaphragm and stomach or spleen on the left, is known as a subphrenic or subdiaphragmatic abscess. The pus usually originates in the upper part of the abdomen, but pus from an appendiceal abscess or a pelvic abscess may be drawn by the respiratory movements to the region below the diaphragm.

The subphrenic region can be divided into six compartments, and the pus may remain confined to one of these (Barnard). Three are on the right and three on the left, the division being effected by the liver and falciform ligament. Two of the three are intraperitoneal, one is retroperitoneal. The right and left *retroperitoneal* varieties of abscess are of less importance than the intraperitoneal. The retroperitoneal pus may come from kidney, liver, spine, pancreas, duodenum, or lung.

The *intraperitoneal* spaces are: (1) *Right anterior*, between the anterior surface of the liver and the diaphragm, and bounded internally by the falciform ligament. It is an upward prolongation of the main peritoneal cavity in front of the liver. The pus usually comes from an in-

flamed appendix. (2) *Right posterior*, bounded by the liver in front, the kidney behind, and the duodenum internally. It is the subhepatic or right kidney pouch, and is infected from a perforated duodenal ulcer. (3) *Left anterior*, lying in front of and above the stomach and occupying the left vault of the diaphragm. It is infected from a gastric ulcer on the anterior surface of the lesser curvature. (4) *Left posterior*, the upward extension of the lesser sac of peritoneum. It is infected from a gastric ulcer on the posterior aspect of the stomach.

A third of all the cases are due to perforation of a gastric or duodenal ulcer, then come appendicular abscess and abscess or hydatid disease of the liver; finally there is a miscellaneous group of inflammatory lesions in the kidney, bowel, pelvic organs, pleura, and lung.

The gastric cases occur on the left, the duodenal and appendicular cases on the right side. The abscess is usually intraperitoneal. It may be outside the peritoneum in hepatic cases, renal cases, and those cases of appendicular abscess in which the infection spreads upwards in the cellular tissue behind the ascending colon.

The abscess may contain only pus, or pus and gas combined. The gas may be derived from a hollow viscus, or may be a result of bacterial decomposition. An abscess on the left side nearly always contains gas derived from the stomach. The chief infecting organism is B. coli.

The physical signs may be complicated by an upward extension of the process through the diaphragm giving rise to a serous pleurisy or an empyema. If gas is present in such a case it is possible to distinguish four zones superimposed one on top of the other, as follows: (1) a zone of lung resonance, (2) a zone of pleural effusion dullness, (3) a zone of gas resonance, (4) a zone of abscess dullness. The diaphragm is displaced upward on the affected side, as may be beautifully demonstrated by the X-rays, and the liver may be pushed downwards.

A subphrenic abscess is a steadily progressive condition. The abscess may burst into the pleural or the pericardial sac, or into the general peritoneal cavity.

TUBERCULOUS PERITONITIS

Tuberculosis of the peritoneum is commonest in children and young adults. It may occur, however, at any age, and Osler considers that there are more cases over than under the age of twenty.

As regards sex the statistics vary, depending upon whether they are operative or postmortem. The former show females to be more frequently affected, the latter males. This may be because females come more frequently to operation, but less frequently to autopsy.

The disease may appear in either of two great forms, acute miliary tuberculosis and chronic tuberculosis.

Acute Miliary Tuberculosis of the Peritoneum.—This is merely a manifestation of a general miliary tuberculosis, usually secondary to tuberculosis of the lungs. The local condition is often overlooked owing to the dominance of the constitutional symptoms, or it may be mistaken for typhoid fever. The patient is likely to die of tuberculous meningitis.

Chronic Tuberculous Peritonitis.—For practical purposes the disease may be regarded as always secondary to some tuberculous focus else-

where, although it is conceivable that the bacilli might pass through the wall of an inflamed bowel and infect the peritoneum.

There are three chief sources of infection: (1) tuberculous ulceration of the bowel, (2) a tuberculous mesenteric gland, and (3) tuberculosis of the Fallopian tube. The last named is one of the most important sources, and is responsible for a large number of the cases in females. It often happens that the peritonitis persists in spite of treatment, until the tube which is a constant source of reinfection is removed.

Apart from these principal sources the infection may spread from the lung or pleura by way of the lymphatics, or from a distant focus in the bones, joints, or bronehial glands by way of the blood.

Chronie tuberculous peritonitis manifests itself in two main forms: (1) a moist form, in which there is marked fluid exudation, so that this variety is often called the exudative form, and (2) a dry form, characterised by the formation of adhesions and matting of the viscera, often known as the adhesive form. Naturally intermediate forms are common, so that there may be a considerable fluid exudate with numerous adhesions. On the whole, however, the exudate appears to inhibit the formation of adhesions. The exudative form is more charaeteristic of a more acute infection, as the toxins present do not favor fibrous formation.

The Moist Form.—The disease comes on insidiously, the patient loses strength and weight and wastes away, the abdomen becomes progressively enlarged. In the late stages the clinical picture is very striking, the wasted emaciated frame of the patient, often a child, surmounted by a vast, tense, shiny abdomen over which course numerous distended veins.

When the abdomen is opened it is found to be filled with fluid. This fluid is thin, and of a lemon-yellow or sometimes a greenish color. Its fibrin content is usually low, few or no flakes of fibrin may be seen, but occasionally it may coagulate spontaneously. It often contains some blood, and red cells and lymphocytes are present in the centrifuged deposit. Blood-stained ascitic fluid should always suggest carcinoma or tuberculosis of the peritoneum, although the blood is much more abundant in the former than in the latter. The specific gravity varies from 1.019 to 1.026. The albumin content is between 4 and 7 per cent.

The fluid having escaped, the entire surface of the peritoneum is seen to be studded with fine tubercles about the size of a pin's head. Around and between these there is a varying amount of peritoneal reaction as evidenced by congestion of the vessels and an inflammatory exudate. The latter may in some cases become so abundant as to cover up the tubercles, and eventually cause extreme thickening of the walls of the organs affected.

Not all of the tubercles are miliary in size. Some may be as large as a hazel nut. Masses of enlarged, and it may be caseous, mesenteric glands, impalpable before owing to the presence of the fluid, are often found. The omentum may be greatly infiltrated, thickened, and crumpled up so that it forms a flat mass like a pancake or a rounded one like a sausage which can be felt running transversely across the abdomen. This, however, is more characteristic of the adhesive variety.

A tuberculous lesion may be found, and should always be looked for, in the tubes and ovaries. It is important, however, not to mistake the

small subserous cysts so frequently seen on the exterior of the tubes for miliary tubercles, an error easily committed by the uninitiated. The lack of any reaction around them and their transparent character readily serve to distinguish them from true tubercles.

The encysted form of tuberculous ascites is usually found in women, but is much rarer than the diffuse variety. The condition is due to a combination of the dry and moist forms, the fluid becoming localized by the formation of dense adhesions. It is of considerable clinical importance, as it is so readily mistaken for an ovarian, parovarian, or other abdominal cyst.

The Dry Form.—In this variety there is little or no effusion, the main characteristic being the formation of a dense inflammatory exudate with numerous adhesions and great matting of the viscera. Even in the fluid form there may be some tendency towards the formation of adhesions.

The deposition of fibrin most readily occurs, when there is just enough fluid to fill in the spaces between the sulci, and when the infection is not sufficiently severe for much toxin formation. Although the adhesions become organized they are seldom converted into fully formed fibrous tissue, for when stained by Van Gieson's method they continue to take the picric acid rather than the fuchsin stain.

The coils of bowel are inextricably matted together. The surface may be studded with tubercles, or they may be obscured by the exudate, which often causes such great thickening that they may be confined to the subperitoneal tissue, no tubercles appearing on the surface. This is most marked when the primary area of infection is limited, and is best seen in the region of the cecum and the appendix.

The pancake thickening of the omentum is particularly marked in this form. Caseous masses of considerable size may be formed. A fecal fistula is of fairly frequent occurrence. This may be formed by a loop of bowel becoming adherent to the abdominal wall, and ulceration destroying both the wall of the bowel and the abdominal parietes, or a caseous focus may ulcerate into the bowel, and later establish a communication with the surface. In children the fistula often opens at the umbilicus.

The prognosis is not so gloomy as that held by the older writers ("la terminaison constante des affections tuberculeuses de péritoine est le mort"—Aran), nor yet is it so rosy as some recent surgical statistics would imply. Opening the abdomen and draining the fluid does indeed produce a wonderfully beneficial effect in the cases with ascites, although the exact mechanism of the improvement is by no means clear. Many such cases, however, although hailed as surgical cures die later of tuberculosis elsewhere. Much depends on the possibility of removing the primary focus. When this is in the Fallopian tube excellent results have been obtained. Conservative treatment alone is successful in a number of cases. Surgical treatment is of course demanded for such complications as intestinal obstruction and abscess formation.

Lycopodium Peritonitis.—Lycopodium spores in the dusting powder of surgical gloves may cause a localized peritonitis with the formation of adhesions or of surface nodules. The spores have short spinous processes which cause them to adhere to the peritoneal surface. They excite a chronic inflammatory reaction with the formation of a *lycopodium*

granuloma. Such a granuloma may of course develop in surgical wounds not connected with the peritoneum. There may be large numbers of small nodular lesions over the surface of the peritoneum, a condition easily mistaken for tuberculous peritonitis or carcinomatosis. The lesions consist of lymphocytes, plasma cells and foreign body giant cells (Fig. 35). There is some necrosis, followed later by extensive fibrosis. The spores, which are often contained within the giant cells, stain faintly with eosin so that they are easily overlooked in necrotic areas, but they are acid fast, and stain a bright red with the Ziehl-Neelsen method. They are of large size, averaging 30 microns in diameter. Similar lesions are produced by talc powder, which consists of crystals of magnesium silicate, and appear as refractile bodies in the lesion.

TUMORS OF THE PERITONEUM

Various forms of primary new growth of the peritoneum have been described, of which the most distinct is the endothelioma. These tumors are so rare and doubtful that they need not detain us here.

In considering tumors of the peritoneum it will be convenient to include a number of conditions affecting neighboring structures, especially tumors of the retroperitoneal tissue. The commonest and most important tumors are those secondary to carcinoma of the abdominal organs.

Carcinoma.—Carcinoma of any organ in the abdomen or elsewhere may set up metastases in the peritoneum. The commonest source is the stomach, the next most common is the ovary. Ascites is a frequent accompaniment, and the fluid is usually blood-stained from hemorrhage. Large epithelial cells may occasionally be found in fluid obtained by puncture. These may suggest malignancy, as in tuberculous ascites the chief cell is the lymphocyte.

The disease may spread in three distinct ways, so that three varieties may with convenience be distinguished: (1) by direct extension, as in scirrhous or colloid tumors of the stomach and bowel; (2) by superficial dissemination, as in papillary cystadenomas of the ovary and some cancers of the stomach; (3) by the blood stream, or lymphatics, as in diffuse carcinomatosis.

Direct Extension.—Carcinoma of the stomach and bowel usually involves the peritoneal coat sooner or later, and large masses may be formed, particularly in the great omentum and in the gastro-hepatic omentum. When the primary tumor is a colloid cancer the secondary growth may attain a great size, accurately reproducing the original structure.

Extension by Dissemination.—A malignant growth may rupture and disseminate carcinomatous particles throughout the peritoneal cavity. These become implanted on the surface of the peritoneum and may grow to a considerable size, although usually they remain small. Again the original structure is faithfully reproduced.

The best example of this variety is afforded by a papillary cystadenoma of the ovary, the papillary processes of which rupture the capsule and become widely disseminated. A remarkable feature of the condition is that in rare cases removal of the mother tumor may be followed by spontaneous disappearance of the daughter ones.

A carcinoma of the stomach setting up secondary growths in the ovaries

does so by shedding cancer cells downwards through the peritoneal cavity. In one of our cases the little nodules could be traced down the peritoneum from the stomach to both ovaries, like the paper scent scattered by the hounds in a paper chase.

In all of these cases malignant cells may be found in the ascitic fluid which is so constantly present. The diagnosis should be made on the arrangement of the cells, not on their individual appearance. The pathologist should therefore have recourse not to smears but to the histologic sections of the centrifuged deposit.

A curious variety of this condition is *pseudomyxoma peritonei*. This follows the rupture either of a pseudomucinous cyst of the ovary or of mucous cysts of the appendix. The ovarian cases are by far the more common. Large gelatinous masses, more or less encapsulated, are formed, which may penetrate every part of the peritoneal cavity, even into the space between the liver and the diaphragm, and sometimes produce enormous distension. When the abdomen is opened large globular masses of mucoid material roll out, and can be scraped off the surface of the viscera. The material is so viscid that it can be pulled out into strings and cut off with scissors. It is of the color of honey, and resembles masses of frog's spawn.

The exact mode of production of this material is not certain. Either the tumor cells become implanted on the peritoneal surface, and there reproduce the gelatinous material of the original growth, or the physical presence of the material acts as an irritant to the peritoneum and causes it to react by a further production of similar masses. The former view appears the more probable, but the chief objection to it is that in many cases no cells can be found, and even when they are present they appear ludicrously inadequate to the production of such enormous masses. It must be remembered, however, that in such a condition as colloid cancer where the mucoid material is undoubtedly produced by cells it may be extremely difficult to demonstrate these cells owing to the profound degeneration which is the salient feature of the condition.

The peritoneum shows signs of reaction to irritation. A fine pellicle of fibrin is formed over the mucoid material, which later becomes organized to form a thin vascular membrane. Fine fibrous septa are sent up by the peritoneum between the lobulations of the masses; these branch like a tree and enclose spaces in which the material lies. It is on this account that the masses may prove so difficult of separation. What epithelial cells are present are tall columnar, and show such profound degeneration that it is easy to believe that they will soon disappear.

The prognosis is bad. The majority of cases ultimately prove fatal, although it may not be for a number of years. Removal of the primary growth may check the disease, especially when the appendix is the source of the trouble. Recurrence, however, may be expected. Many cases die because of sepsis and embolism.

Extension by Blood Vessels and Lymphatics.—Diffuse carcinomatosis, which may have its origin in any epithelial organ, will involve the peritoneum in common with the rest of the body. The entire surface, both parietal and visceral, may be studded with small growths. In one such case we found that the metastases were sprinkled as from a pepper pot.

These minute metastases are easily mistaken for miliary tubercles, and when the abdomen is opened it may be difficult for the surgeon to decide with which he is dealing. The tubercles are often oblong and may show tiny nodosities on the surface; the carcinomatous nodule, growing expansively, is spherical, free from nodules, but may show slight umbilication. In carcinoma, moreover, there will usually be some masses too large to be called tubercles. The ascitic fluid in tuberculosis contains large numbers of lymphocytes, whereas in malignant disease large epithelial cells may occasionally be found which will give a clue to the diagnosis.

Lymphatic spread may result in widespread dissemination. At autopsy it may be difficult to decide if multiple peritoneal growths should be regarded as implantations or as due to blood or lymph spread. When there is extensive involvement of the mesenteric lymph nodes, and especially when the wall of the bowel presents a fine network of white lines, spread is evidently by way of the lymphatic system, for the white lines are lymph vessels distended by tumor cells.

Retroperitoneal Tumors.—Under this heading it would be possible to include tumors arising from the kidneys, adrenals, pancreas, and other retroperitoneal organs. In practice the term is confined to tumors growing from the connective tissue, particularly that behind the peritoneum of the posterior abdominal wall.

These tumors are of varied character, and are by no means readily collected into groups. We may distinguish the retroperitoneal lipoma and the retroperitoneal sarcoma.

Retroperitoneal Lipoma.—Although this tumor is commonly known as a lipoma it is extremely doubtful if it merits such an innocent name. For it does not consist only of fat; myxomatous areas and even sarcomatous areas may be discovered if a number of different parts of the growth be examined. Extensions existing either as arms of the parent mass or as definite separate growths are not uncommon. At a recent autopsy on an obscure case of paraplegia the pelvis was completely filled by an apparently innocent lipoma. On further investigation it was found that the lipoma was creeping through several of the intervertebral foramina and severely compressing the cord. Only after sections had been cut from many parts of the tumor was one found which showed definite sarcomatous characteristics. There may be firm adhesions to surrounding structures. Finally, removal of the tumor may be followed by recurrence. All these facts go to show that though the tumor may be called a lipoma it should be approached by the surgeon with a very considerable degree of respect. The consensus of opinion, indeed, points to these growths being allied to the teratomata rather than to the innocent lipoma.

The tumor usually appears in middle age, but may begin in early childhood. It is commoner in women than in men. It commences as a rule on either side of the vertebral column about the level of the kidney. Growing very slowly it may reach an enormous size, and be accompanied by profound emaciation of the patient. Almost the entire abdominal cavity may be filled by the tumor. One case is on record in which the tumor was sixty-three pounds in weight. When the abdomen is opened a yellow, lobulated mass of varying size is seen pushing the colon in front of it. It may insinuate itself between the leaves of the mesentery, so as to have

the appearance of being primarily a mesenteric tumor. Removal may be easy, or very difficult owing to the adhesions and extensions already referred to. .

Microscopically the greater part of the mass consists of adipose tissue, but, as already mentioned, here and there may be found areas of myxomatous tissue and of sarcomatous formation. It appears probable that these have developed primarily and that the tumor represents an embryonal type of tissue, rather than that they are due to a transformation of the lipoma.

Retroperitoneal Sarcoma.—This tumor arises from the fascia of the posterior abdominal wall, usually in the same position in which lipomata occur. Teratomata, lymphosarcomata, the enlarged retroperitoneal glands of Hodgkin's disease, and sarcomata of the retroperitoneal organs should not be included in this group. It appears probable from recent work that many so-called retroperitoneal sarcomas may really be neuroblastomas.

It is a disease of middle life, insidious in onset like the lipoma, and equally difficult of diagnosis. Fixity is one of the chief characteristics of both the lipoma and the sarcoma.

Usually soft in consistence, the smaller growths may be fairly firm. The cut surface is pinkish white. Areas of softening with hemorrhage or cyst formation are common. Microscopically the tumor is fibrosarcoma or round-cell sarcoma.

CYSTS OF THE MESENTERY

A variety of cystic formations may occur in the mesentery or the omentum. Of these the more important are enterogenous cysts, lymphatic cysts, gas cysts, dermoid cysts, and echinococcus cysts.

Enterogenous Cysts.—These are derived from diverticula of the intestine in which the communication with the bowel has been pinched off. Intestinal structures can often be demonstrated in the wall of the cyst. There may be intestinal epithelium or muscle resembling that of the intestinal wall.

Lymphatic Cysts.—These cysts are probably similar in nature to the lymphatic cysts of the neck and axilla, and may therefore be regarded as lymphangiomata of congenital origin. They occur in the earlier years of life, seldom over the age of thirty. Usually single, in some cases a number of cysts may be present. They may be present in any part of the mesentery, but usually in the root. They may attain a great size, but as a rule are no larger than an egg. Their mobility distinguishes them from retroperitoneal tumors, but they may closely simulate an ovarian cyst with a long pedicle.

The wall is composed of fibrous and elastic tissue, and the cavity is lined by a flat endothelium. The contents may be watery, milky, or bloody from hemorrhage. As a rule they are quite clear.

Gas Cysts.—In rare instances there may be gas cysts of the mesentery. These are usually quite small, and they are found clustered along a segment of the bowel (Fig. 238). In a specimen in the University of Manitoba Medical Museum the cysts are about the size of a pea. Very similar cysts are of frequent occurrence in the pig. Finney, describing a case of his own,

Fig. 238.—Gas cysts of the mesentery.

Fig. 239.—Hydatid cysts of the omentum.

considers that the cysts are probably neoplastic, arising in a connective tissue tumor the cells of which have gas-forming properties. Others think that the gas is produced by bacteria. Giant cells with very numerous

nuclei (sometimes as many as 50 or 60) may be present, and it is around these that the air spaces are formed. The gas is odorless and does not burn.

Dermoid Cysts.—These may be situated within the layers of the mesentery. More frequently, however, they are retroperitoneal in position. Many of these structures may be called teratoid mixed tumors, and often represent all three of the embryonal layers.

Hydatid Cysts.—Hydatid cysts of the peritoneum or the retroperitoneal tissue are not uncommon. They may form multiple masses of considerable size (Fig. 239). Usually the correct diagnosis is not made until the cysts have been opened and the hooklets discovered.

PERITONEAL ADHESIONS

The formation of adhesions between two peritoneal surfaces is essentially a beneficent process. Without it abdominal surgery would be impossible, the gastro-intestinal canal could never be opened, every local inflammation would become general, every perforation would prove fatal. These remarks are perhaps necessary in view of the attitude sometimes adopted by operators and by the general public towards adhesions, and the tendency to attribute all kinds of symptoms to this cause.

Hertzler has shown that in a clean peritoneal wound an exudate is laid down a few minutes after the peritoneal surfaces are sewn together. In 10 minutes bundles of fibrin appear, and in a few hours these are fully developed. Subperitoneal edema brings the serous surfaces closer together. Fibrin is formed into fibrous tissue about the third or fourth day and this becomes adult connective tissue by the end of a week. The muscular and mucous coats of the bowel require several weeks for thorough healing. Sepsis, undue trauma, etc., naturally interfere with this sequence.

Adhesions may be temporary—they usually are—or permanent. They may be caused (1) by chemical irritation, (2) by mild forms of inflammation, or (3) by mechanical violence.

Adhesions Due to Chemical Irritations.—Almost any chemical irritant, provided it be not too strong, may set up the formation of adhesions. In the days when antiseptics were freely applied to the peritoneal surface adhesions were of frequent occurrence. Iodine is probably responsible in many cases. Suture material soaked in an antiseptic may act in the same way. The escape of the gastric contents as the result of perforation may be attended by adhesion formation at a considerable distance from the perforation.

Adhesions Due to Mild Inflammation.—Adhesions may be found at the site of the pathological lesion producing mild inflammation, or at a distance when the inflammation is more acute. Examples of the former are seen in the adhesions around a gall bladder containing stones, or at the seat of a chronic gastric ulcer. The inflammation spreads outward till it involves the peritoneal coat, fibrin is formed, and fibrous adhesions of a permanent character result preventing the occurrence of such an untoward complication as perforation into the general peritoneal cavity.

When the inflammation is more acute and virulent in character, the exudate is cellular, no fibrin is formed, and adhesions are absent. At some little distance, or it may be a considerable way off, the violence of the

process diminishes, and the reparative formation of fibrin becomes possible. At the seat of an appendiceal abscess there may not be a single adhesion, but abundant adhesions may be formed at a distance. A healed gastric ulcer may be associated with adhesions between the omentum and the abdominal wall, and between the gall bladder, liver, and abdominal wall.

The nature of the infecting organism may have an important bearing on the formation of adhesions. The most extreme instances of adhesions are seen in gonococcal infection of the Fallopian tubes. The gonococcus acts as a comparatively mild irritant, and enormous quantities of fibrin may be produced which become converted into permanent adhesions, binding the tubes, ovaries, and uterus into one inextricable mass. Reference has already been made to the "violin-string" adhesions between
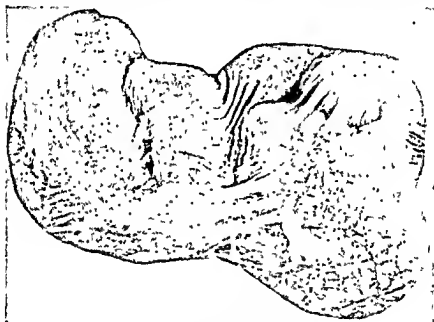
Fig. 240.—Old intestinal adhesions causing obstruction.

the liver and the anterior abdominal wall or diaphragm. The pneumococcus and the staphylococcus excite great fibrin formation, but the adhesions are more apt to be temporary. The colon bacillus tends to excite fibrin formation, but to dissolve fibrin once formed. The virulent streptococci render the protective formation of fibrin an impossibility, so that the infection always becomes diffuse.

The majority of what may be called inflammatory adhesions are temporary and disappear when their work is done. Some become vascularized and converted into true fibrous tissue (Fig. 240). Even these fibrous adhesions, however, tend to become stretched owing to traction, and to decrease in size. A broad band of adhesions may, when the abdomen is opened again a few weeks later, have shrunk to a mere fibrous cord, which may eventually give way. There is no evidence that, as Lane sug-

gests, adhesions may grow stronger owing to continued traction. An adhesion is merely a scar, and no scar behaves in this way.

Adhesions Due to Mechanical Violence.—A blow on the abdomen may produce sufficient irritation to cause the formation of adhesions. If the violence be sufficiently great, even temporary adhesions may not form, the wall of the bowel becomes necrosed, and perforation a few days later is the result.

The principal cause of permanent adhesions is the injudicious activity of the surgeon. When the peritoneum is incised the cut edges invite the formation of adhesions. It is only when the edges are sutured so that the suture line alone is presented to the peritoneal cavity that this complication can be avoided. An uncovered stump, such as that of the appendix, cannot fail to form adhesions.

If the epithelial layer of the peritoneum is destroyed adhesions are certain to form. For such abrasion to occur a considerable degree of violence is needed. Vigorous rubbing with the finger covered by gauze is insufficient to destroy the continuity. It is true that such rough handling will produce an inflammatory response, but without the formation of adhesions, for the response disappears when the irritant is withdrawn. The omentum is the part of the peritoneum most sensitive to this type of injury.

When the entire thickness of the peritoneum is destroyed, as by means of a cautery, the tendency to adhesion formation on the part of the underlying muscle is comparatively slight.

It is undoubtedly the case that in some individuals there is a peculiar predisposition to the formation of adhesions. As the result of an operation numerous adhesions are formed, which, on being broken down at a subsequent operation, only reform once more. As Hertzler puts it: "This sequence lasts as long as the patient does, or the hopeful persistence of the surgeon endures." Even in a normal person the frayed edges of broken-down adhesions form an ideal starting point for the formation of fresh adhesions.

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THE UPPER URINARY TRACT

THE KIDNEYS

A patient suffering from renal disease (apart from Bright's disease) is likely to have one or more of the following symptoms: (1) frequent or painful micturition, (2) pain or tenderness over the kidney, (3) enlargement of the kidney, (4) pus in the urine, (5) blood in the urine.

The conditions most likely to give rise to one or more of these symptoms are: (1) suppuration in the kidney, (2) tuberculosis, (3) stone, (4) hydronephrosis, (5) tumor.

Other conditions to be borne in mind are cysts of the kidney, developmental defects, and perinephritic abscess.

SUPPURATIVE INFECTIONS OF THE KIDNEYS

There are three possible routes by which pyogenic bacteria may reach the kidney: (1) by ascent from the bladder and urethra, (2) by descent from the blood stream, (3) by direct extension from neighboring organs, especially from that cesspool of the body, the cecum, the route being along the lymphatics.

As is the way in medicine, first one and then another of these paths has been the favorite of the hour.

For long the ascending route was regarded as the only one worthy of serious consideration. It was pointed out that the pelvis of the kidney was really in direct communication with the outside air, and that, particularly in the female, there was little to prevent pathogenic bacteria from travelling up this path. Later, however, it was recognized that the gonococcus is the only organism which has acquired the art of climbing up the healthy urethra, and that, as has already been seen in the case of the gall bladder, an epithelium-lined duct offers remarkable resistance to such passage.

Direct invasion of the kidney via the lymphatics by the teeming inhabitants of the large intestine has been suggested, but no convincing evidence of this occurrence has ever been brought forward. It is true that direct extension from a neighboring focus of infection may occasionally occur, and bacteria may be introduced from without by penetrating wounds, but these are rare occurrences in clinical practice.

To-day the prevailing view is that the common route of infection is by the blood stream, except in stricture of the urethra, enlargement of the prostate, and paralysis of the bladder, in which conditions an ascending infection readily occurs owing to stagnation of the urine.

Descending Hematogenous Infection.—Far from being a rare occurrence it is probable that hematogenous infection of the kidney is comparatively frequent. The kidney is one of the main filters of the body, and any bacteria gaining access to the blood stream are naturally elimin-

ated by this route. There is reason to believe that bacteria are constantly invading the blood stream in small numbers. They are absorbed from two sources:—

(1) Small focal abscesses, notably in the tonsils and at the roots of the teeth.

(2) Mucous membranes in a catarrhal condition, notably the mouth and the large bowel.

These bacteria are carried to the liver and kidney. Three things may happen to bacteria carried to the kidney. (1) They may be destroyed by renal epithelial cells. (2) If in large numbers they may be excreted in the urine, as in typhoid fever. (3) They may be retained alive as prisoners, in which case alone they will produce inflammation of varying degrees of severity.

Should the inflammation be acute its presence is readily detected. Often, however, it is of such low grade as to betray itself by no clinical manifestation. Such a kidney remains in a damaged condition, and at any time the infection may be lit up, or a fresh infection may be superimposed on the weakened kidney. A similar series of events is well recognized in the case of the appendix and the valves of the heart.

Bacterial infections of the kidney are due to:—(1) the pyogenic cocci, and (2) Bacillus coli. These attack different parts of the kidney.

The pyogenic cocci involve the kidney filter and produce abscesses in the cortex. They lodge particularly in the glomeruli, where they may form large masses readily seen under the low power of the microscope. Their pathogenicity is high, and they rapidly produce suppuration. The urine, apart from a trace of albumin and a few pus cells and red blood corpuscles, may show little evidence of the severe nature of the infection. It is alkaline in reaction, owing to the ammoniogenic power of the bacteria.

Bacillus coli lodges in the pelvic portion of the kidney, although later the infection may extend into the cortex. The urine is loaded with pus, and is usually strongly acid in reaction. The pathogenicity of Bacillus coli is lower than that of the pyogenic cocci, and a chronic infection may linger for years in the renal pelvis. At intervals recurrent invasion of the kidney from the pelvis may occur, so that in time the greater part of the kidney may become involved. These invasions may occur along the line of the tubules, but it is more probable that the common route is by the lymphatics in the interstitial tissue.

The overwhelming majority of kidney infections are due to Bacillus coli. In a series of 135 cases examined by Frank Kidd 117 were due to B. coli, 9 to streptococci, 7 to staphylococci, and 2 to the gonococcus.

Ascending Infection.—The only organism which has acquired the power of ascending the healthy urethra is the gonococcus. No other organisms can ascend the healthy ureter. Bacteria introduced into the normal bladder quickly disappear and produce no ascending infection.

When there is urinary stasis due to stricture of the urethra, enlargement of the prostate, or obstruction to the ureter bacteria readily make their way from the bladder to the kidney. Theoretically they may do so by three routes: (1) by ascending in the lumen of the ureter; (2) by passing up the lymphatics in the wall of the ureter; (3) by reaching the kidney through the blood stream.

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The obvious route is the intraureteral one. The picture of a colon bacillus swimming up the stream of stagnant urine with vigorous strokes of its flagella is one which appeals to the imagination. It is doubtful if in practice this ever occurs. Even in the case of the infection which so promptly follows implantation of the ureters into the rectum it can be shown that the infection passes up outside rather than within the walls of the ureter.

There is more to be said in favor of the lymphatic route. The mucosa and submucosa of the bladder are supplied with an extensive network of lymphatics which, passing up in the wall of the ureter, communicate with those of the kidney. Bacteria placed on the urethral mucosa pass into the lymphatics and up the walls of the bladder and ureter, congregating in the lymphatics under the capsule of the kidney. From this position, however, they do not infect the kidney nor appear in the urine. Instead, they pass through the lumbar glands, and by way of the thoracic duct they enter the blood stream. Dye injected in rabbits in different areas of the bladder wall, different levels of the lower ureteral wall, and the cervix, is absorbed and passes to the common iliac group of glands (MacKenzie and Wallace). It then passes upwards toward the thoracic duct and probably to the blood stream and kidneys. There is no absorption from the healthy bladder mucosa.

Whatever may be true for experimental infections there can be little doubt that in practice the route of election in ascending infection is via the lymphatics direct to the blood stream and thus to the kidney. The rigor of "eatheter fever" is due to the passage of bacteria through the walls of the urethra and thence by the lymphatics to the blood. Although, therefore, the infection is in a sense ascending, it is even more truly a hematogenous one. Barrington and Wright have shown that invasion of the blood stream is a common occurrence following operations on the urethra, and this invasion can be detected in the course of a few minutes. Similar invasion may occur at a later date after natural micturition.

Predisposing Causes of Hematogenous Infection.—When an overwhelming dose of bacteria is presented to a healthy kidney, resistance is broken down and infection will result. In such a case the infection is always bilateral. When, however, the bacteria are in smaller numbers the existence of some pre-existing accessory cause will determine whether or not an infection will be set up, and which kidney will be affected. As Kidd remarks in the opening sentence of his book on Common Infections of the Kidneys, "bacteria are not *the* cause of bacterial infections."

The chief of the accessory causes are retention and trauma.

Retention may be due to a variety of conditions which need not be enumerated here, affecting either the urethra or the ureter. It is not so much the presence of retained urine in the renal pelvis as the congestion consequent upon the damming back which is the factor of importance.

Trauma.—Many traumatic injuries of the kidney of so slight a character as to give rise to no symptoms may predispose the organ to infection by pyogenic bacteria circulating in the blood. Of greater importance is the trauma produced by the presence of a stone in the renal pelvis. At the same time it must be recognized that a stone may be the expression rather than the predisposing cause of an infection.

Types of Renal Infections.—In so complex an organ as the kidney it may be somewhat artificial to divide the lesions into separate groups. Infection of the kidney will involve the pelvis, infection of the pelvis will spread into the kidney. For purposes of description, however, it is convenient to consider the following types: 1. diffuse suppurative nephritis; the pyemic kidney; 2. focal suppurative nephritis; septic infarcts of the kidney; pyelonephritis; 3. pyelitis; 4. pyonephrosis.

DIFFUSE SUPPURATIVE NEPHRITIS

The lesions in this condition are not confined to the kidney, but are scattered throughout the body. It is merely one manifestation of a general condition of pyemia. Owing, however, to the peculiar anatomical arrange-
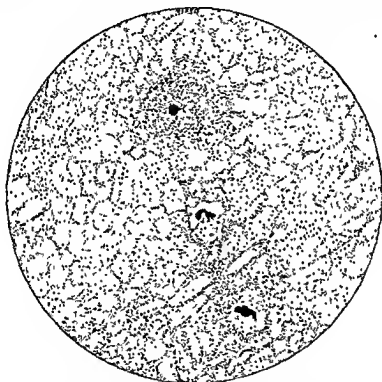
Fig. 241.—Diffuse suppurative nephritis; pyemic abscesses in kidney. In the center of each abscess there is a mass of bacteria.

ments of the kidney favoring the retention of emboli, in some instances the kidney alone will be involved in addition to the primary source of the infection. That source in many cases is an ulcerative endocarditis, and the infecting organisms are staphylococci or streptococci.

In subacute bacterial endocarditis caused by the Streptococcus viridans a peculiar lesion is found confined to the glomeruli, and not proceeding to suppuration.

Both kidneys are always involved in pyemia. During life they are considerably enlarged, red, hot, and steaming. The capsule, which may be tightly stretched, peels off with ease, leaving a surface dotted with minute, opaque, yellowish elevations, each of which is surrounded by a zone of

congestion. These elevations represent minute abscesses, many no more than pin-point in size. The diffuse widespread arrangement should suggest the embolic nature of the infection. In the focal variety the abscesses tend rather to be arranged in little groups here and there.

On section the surface of both kidneys is sprinkled with numerous minute abscesses. These are most abundant in the cortex, where they are circular in shape. They also occur in the medulla, but there they take the form of elongated yellowish streaks. The cortex is pale and swollen. The pelvis is seldom affected.

Microscopically each abscess consists of a mass of polymorphonuclear leucocytes. Masses of bacteria can be demonstrated in the earlier cases occupying the glomerular and the peritubular capillaries (Fig. 241). The interstitial stroma in the neighborhood of the abscess shows marked round-celled infiltration. The epithelium of the tubules manifests varying degrees of degeneration and necrosis.

FOCAL SUPPURATIVE NEPHRITIS OR PYELONEPHRITIS

The term pyelonephritis signifies inflammation of the kidney and renal pelvis. Pyelitis indicates inflammation confined to the renal pelvis, but it is doubtful if such a condition exists. The pelvic inflammation is secondary and not an integral part of the process. Chown has shown that even in the so-called pyelitis of infancy the essential lesion is in the kidney rather than in the pelvis. Some such name as pyonephritis would be preferable to pyelonephritis.

The renal infection may be obviously hematogenous in origin, or it may ascend from below. An ascending infection is particularly common in infancy, pregnancy, and over the age of fifty due to prostatic enlargement in the male and cancer of the cervix in the female. Bacillus coli is the common infecting organism, but the pyogenic cocci are frequent in hematogenous infections. The element of obstruction is of the greatest importance in determining the outcome. G. K. Mallory and his co-workers showed this by injecting colon bacilli intravenously into rabbits in which one ureter had been partially ligated; acute *pyelonephritis developed in the obstructed kidney in 75 per cent of the animals, but never in the unobstructed kidney*. Release of the obstruction after a few days induced healing of the pyelonephritic process. In man the question of whether a blood infection will cause unilateral or bilateral renal lesions is probably largely dependent on the presence or absence of obstruction. In ascending infection some element of obstruction in the urinary tract is likely to be present from the beginning.

Within recent years our concept of pyelonephritis has undergone a great change. It used to be regarded as an acute infection which either cleared up quickly or developed into a progressive condition with eventual destruction of the renal parenchyma. It is now known that the apparent recovery may be misleading, that the disease may pursue a slow insidious course sometimes without any initial acute attack which can be recognized, that the end stage may be one of chronic renal insufficiency with uremia, *i. e.*, a variety of Bright's disease, and that there may be an associated arterial hypertension apparently dependent on the renal condition. As pyelonephritis is sometimes unilateral, the tempting pos-

sibility presents itself of removing the offending kidney and relieving the hypertension. A number of cases have been published in which permanent relief has been afforded, but it is probable that for every one published success there are ten or twenty failures of which nothing is heard. The relief of the hypertension often lasts only a few weeks or months, after which the blood pressure regains its former level.

Gross Appearance.—This varies extremely with the stage of the disease. As a rule both kidneys are involved, but the lesions are often much less advanced in one than in the other. They may be focal or diffuse. In the acute stage the kidney is swollen and congested, and the pelvis is of a bright red color and filled with pus. Under the capsule there are numerous yellow spots representing areas of suppuration, as well as dark irregular patches which form the base of wedge-shaped areas in the renal substance. The superficial lesions are often raised above the surface as small pustules. If healing occurs later they are represented by depressed U-shaped scars.

The cut surface shows patchy areas of suppuration which tend to be spherical in the cortex and linear in the pyramids (Fig. 242). Wedge-shaped areas of larger size may be suggestive of infarcts, but merely represent upward extension of the infection. If suppuration is progressive, abscess cavities are formed with gradual destruction of renal tissue. The outline of the calyces is destroyed, and the resulting distortion seen in the X-ray film is an important feature in the clinical diagnosis.

The disease may develop in a more gradual and insidious manner with little frank suppuration. The inflammation, which is chronic in character,

Fig. 242.—Pyelonephritis with marked destruction of parenchyma.

extends here and there in the kidney, destroying renal tissue, but being followed later by healing, fibrosis, and contraction. The result is a contracted kidney, on the surface of which there are depressed scars. If these scars are of considerable size they are apt to be regarded as healed infarcts. When they are much smaller the effect is to give the kidney a granular appearance which may be indistinguishable from that of chronic glomerulonephritis or arteriolar nephrosclerosis. This condition is called *pyelonephritic contracted kidney*, and in the past it has frequently been mistaken for these two diseases just mentioned. Chronic and healed pyelonephritis is a much commoner condition than used to be supposed. In distinguishing between chronic pyelonephritis and other conditions with which it may be confused, attention should be paid to the *renal pelvis* (thickened), calyces, and ureter.

The *microscopic picture* varies as much as the gross appearance. There may be many small abscesses and widespread interstitial infiltration with polymorphonuclear leucocytes. Much more usual, however, is a streaky linear round-cell infiltration with an admixture of polymorphonuclears (Fig. 243). In both cases there is destruction of the renal tubules, with gradual replacement by scar tissue. Many tubules are filled with pus cells (Fig. 244). The process is characteristically patchy, and in the intervening areas the tubules are either normal or dilated, lined by flattened epithelium, and filled with pink-staining colloid-like material, so that in places the tissue may resemble the thyroid gland, a picture strongly suggestive of chronic pyelonephritis (Fig. 245). The experimental studies of Mallory suggest that the colloid material may be derived from the nuclear débris of polymorphonuclear leucocytes. The glomeruli may be intact or may show periglomerular

Fig. 243.—Pyelonephritis. The infection is ascending from the pelvis to the cortex.

Fig. 244.—Pyelonephritis; pus cells in renal tubule. × 250.

fibrosis. In the scarred areas they may be completely hyalinized. In the renal pelvis there is round-cell infiltration or fibrosis, a valuable diagnostic feature for the pathologist in quiescent cases. The arteries show two changes: (1) endarteritis obliterans, a fibrous thickening of the intima with narrowing of the lumen, such as may occur in any area of chronic inflammation; (2) a thickening and hyalinization of all the coats of the arterioles and smaller arteries (diffuse hyperplastic sclerosis), a change which is associated with arterial hypertension.

From Goldblatt's experimental work and from the analogy of the hypertension of glomerulonephritis and arteriolar nephrosclerosis it may

be said that the hypertension is associated in some way with renal ische-
mia, which is so marked in advanced cases on account of the scarring and
the arterial changes. This is not the whole answer, however, for of two pa-
tients with equally ischemic kidneys one may have marked hypertension
whilst in the other the blood pressure
is normal. It is probable that there
are constitutional differences in the
patients, but there may also be local
renal differences which have not as
yet been detected. In the pyeloneph-
ritis which is so common after the age
of fifty hypertension is a frequent
accompaniment, but as both condi-
tions are encountered at this period
the element of coincidence cannot be
eliminated. In the pyelonephritis of
childhood, however, the chronic stage
of which was first recognized by
Longcope, this element does not need
to be considered. In some of these
cases hypertension has developed a
number of years after the first attack;
the renal condition is pyelonephritic
contracted kidney.

Fig. 245.—Pyelonephritis: colloid casts in tubules. × 120.

PYONEPHROSIS

This is a condition in which there
is extreme dilatation of the pelvis and
calyces which are filled with thick
creamy pus, associated with great
destruction of the renal parenchyma. The condition may arise in three
ways: (1) progressive suppuration and destruction, often associated with
the presence of a calculus; (2) an infected hydronephrosis, which is less
common; (3) tuberculous pyonephrosis.

The kidney is much enlarged. It is ensheathed in a dense fibro-fatty
layer composed of the perirenal tissue transformed by the inflammatory
process. This is so adherent that it may be impossible to strip it off. The
surface is irregularly lobulated, and on palpation the lobulations are found
to consist of bags containing fluid. When one of these is incised pus of
remarkably thick consistence exudes. This pus contains no living bacteria.
When the pus is washed away a series of intercommunicating cavities
can be seen, representing the dilated calyces which open into the enor-
mously distended pelvis. The renal tissue is thinned to a mere functionless
shell, so that the kidney may with truth be called a bag of pus (Fig. 246).

The commencement of the ureter shares in the general dilatation. In
cases where the ureter is not occluded the cystoscope reveals the very
characteristic picture of a worm-like rope of pus uncoiling itself from the
ureteral opening.

Microscopically hardly a trace of kidney structure can be recognized.

Nothing remains but a confused mass of scar and inflammatory tissue, in which the wreck of a few tubules and glomeruli may now and then be made out.

PERINEPHRITIC ABSCESS
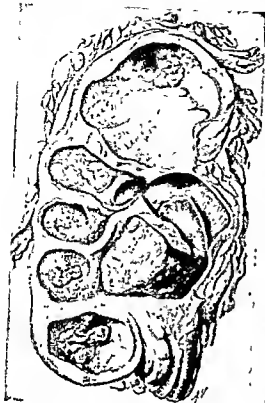
Fig. 246.—Kidney in a condition of pyonephrosis. The dilated pelvis is occupied by a large calculus.

Perinephritic or perirenal abscess may be primary or secondary. It is predominantly a disease of males.

The *primary* form is hematogenous in origin. The infection is carried from some distant focus, usually a boil or tonsilitis. It may follow an acute fever such as scarlet fever. The common organisms are staphylococci and streptococci.

The *secondary* form is the result of pus tracking into the perirenal tissue from some neighboring organ. Usually this is the kidney, but it may be the appendix, pelvic organs or gall bladder. The usual organism is Bacillus coli. The abscess may arise from a *carbuncle of the kidney*. This is a firm, sharply defined mass in the cortex. Although resembling a neoplasm, it is a metastatic staphylococcal lesion, the primary lesion being in the skin (boils). If the infection extends to the surface a perirenal abscess results.

The abscess may be small or may surround the kidney, compressing that organ. The pus may pass up and form a subphrenic abscess, or pass down into the pelvis. Leukocytosis is usually well marked, and pyuria is present in over 50 per cent of the cases.

Two rare inflammatory conditions deserve passing notice.

Pyelitis Granulosa.—This is a chronic inflammatory condition which may affect the pelvis, rarely the ureter or bladder. The wall of the pelvis is studded with little red granules which consist of masses of lymphoid tissue. As a rule they produce no symptoms, but may occasionally give rise to one form of hematuria.

Pyelitis Cystica.—The formation of small cysts as the result of chronic inflammation is much commoner in the bladder than in the renal pelvis. The condition is of no pathological importance.

TUBERCULOSIS OF THE KIDNEY

Renal tuberculosis is never a primary condition. This is a self-evident truth, for the tubercle bacillus has no means of gaining direct access to the

kidney from without. The lesions to which it is usually secondary are tuberculosis of the lungs, lymphatic glands, and bones. As in the similar case of Addison's disease, however, it may occasionally be impossible to demonstrate with certainty any definite active focus elsewhere.

The question whether tubercle bacilli can be excreted by a healthy kidney has long been and still is a debatable one. Large lists of cases have been published showing that in pulmonary tuberculosis there may be an excretory bacilluria without any tuberculous lesions being discoverable in the kidneys. But everything depends on the thoroughness of the search for the lesions. Medlar in an important contribution of experimental renal tuberculosis has shown that tuberculous lesions in the kidney could be found in every case in which there were tubercle bacilli in the urine. He has shown, moreover, that the number of bacilli in the urine bears no relation to the size of the lesions, that in many cases the lesions are microscopic, and that it may even be necessary to employ the method of serial sections. It would appear probable that the conception of an excretory bacilluria should be given up. As a rule, however, these minute lesions heal completely. The real clinical criterion of active progressive renal tuberculosis is the presence of pus and red blood cells in the urine along with the tubercle bacilli, and not the presence of the bacilli alone.

The disease may be of two very different types, the acute or miliary form and the chronic or ulcerative form.

Acute miliary tuberculosis of the kidney is the renal manifestation of general acute miliary tuberculosis. It may be compared with the diffuse suppurative nephritis of pyemia. It is always bilateral, and rapidly proves fatal, the patient usually dying of tuberculous meningitis. The kidneys are slightly enlarged and studded with minute miliary tubercles, but the condition is not one of interest to the surgeon, and need not be described further here.

Chronic or caseo-cavernous tuberculosis of the kidney is a disease of early adult life, being commonest between the ages of 15 and 40. It is always unilateral at the commencement, and may remain so for a remarkably long time. Eventually, however, the other kidney is liable to become involved. The very considerable variations in the statistics given in the literature may be explained by noting that when the diagnosis is a postmortem one the condition will probably be found to be bilateral, whereas a diagnosis made during life will frequently show only one kidney to be infected.

No adequate explanation has ever been given why the condition should at first be unilateral. The kidney cannot be an organ which is specially liable to tuberculous infection, owing to the comparative rarity of the condition. There must be some local predisposing cause. A large number of such causes have been suggested, but the arguments supporting none of them can be regarded as satisfactory. It is distinctly remarkable that there appears to be no relationship between stone and tuberculosis.

Route of Infection.—There are three possible routes by which the kidney might become infected: (1) by the blood stream; (2) by the lymph stream; (3) by direct spread from neighboring diseased organs such as the adrenal or the spine.

Whilst it is possible that in rare cases the second and third routes

may be that adopted by the tubercle bacillus, in the overwhelming majority of cases the infection is hematogenous in origin. Tuberculosis of the urinary tract always commences in the kidney. It never begins in the bladder, and then spreads up the ureter to the kidney.

Site of the Initial Lesion.—The primary renal lesion is nearly always in one of the poles, upper or lower, the intervening parenchyma displaying a remarkable degree of immunity. Tuberculous infection parallels in several respects infection by Bacillus coli. In both the infecting agent passes through the kidney filter, settles down in the collecting portion, and then by a retrograde process passes up the lymphatics so as to infect the cortex. In both the urine is acid. The tendency towards destruction is, however, far greater in tuberculosis than in Bacillus coli infection.

There are two positions in which the process is likely to originate: (1) in the boundary zone at the base of a pyramid; (2) in the apex of a papilla as it projects into the pelvis.

To have reached these positions the bacilli must either have traversed the glomerular capillaries and been carried downwards by the intertubular set of capillaries; or, what is more probable, they have been excreted into the capsular space, passed for some distance along the tubule, and there been arrested.

Subsequent Course.—A miliary tubercle composed of endothelial cells surrounded by a zone of lymphocytes is formed in one of the sites just alluded to. The usual necrosis of tissue occurs, and the focus may ulcerate into the pelvis, with early infection of the ureter, and a resulting tuberculous pyelitis.

At the same time a retrograde process commences, the infection creeping up the lymphatics along the line of the collecting tubules, and eventually infecting the cortex and even the capsule. The progress of the infection is evidenced by yellowish-white streaks in the medulla and similar rounded areas in the cortex. Owing to wide-spread infection of the pelvis and calyces the greater part of the kidney eventually becomes involved in this retrograde process.

Gross Appearance.—The appearance of a tuberculous kidney varies greatly with the extent of the lesions and the degree to which destruction has taken place, so that no one description can be given which will be applicable to every case. We may say, however, that in the early stages small lesions may be observed at the base of the pyramids and a little later in one of the papillae. As involvement of the pelvis occurs at so early a date, the pelvic mucosa will be somewhat roughened and lacking in luster, and the sides of the papillae may be ulcerated.

The later stages are characterized by progressive destruction of renal tissue with cavity formation. The kidney is enlarged, it may be to double the size, and on the surface are to be seen either distinct tubercles or larger bosses denoting cavity formation within. Where the surface is extensively involved there will be adhesions of the perirenal fat. The cut surface shows: (1) caseous yellow tuberculous masses, notably at the base of the pyramids, and at one or both poles; (2) cavities of varying size with rough, ragged walls, containing thick creamy pus without smell and sterile on culture; (3) yellowish lines of infection leading up to clusters of tubercles in the cortex; (4) extensive ulceration and dilatation of the

pelvis with destruction of the papillae; (5) thickening and dilatation of the ureter, although in some cases there may be tuberculous stricture.

One part of the kidney may show early, another part the most advanced lesions (Fig. 247). In the late stages a condition of *tuberculous pyonephrosis* develops, and the kidney becomes converted into a multilocular sac, the various cavities opening into a greatly dilated pelvis, and the whole occupied by thick tuberculous pus (Fig. 248). This material may contain enough calcium salts to give a shadow in the X-ray film. In many cases the condition is due to tuberculous stricture of the ureter; in some

Fig 247.—Tuberculosis of kidney. Every stage of the disease is seen from the earliest lesions in the upper pole to the most advanced in the lower pole.

however, the essential cause appears to be loss of tone of the musculature of the pelvis and ureter, the ureter being dilated along its entire length.

The condition of *closed renal tuberculosis* is one in which the kidney is shut off from the rest of the urinary tract. It is usually due to a sealing-off of the renal pelvis or the ureter. The disease may go through all its stages to complete destruction of the kidney without any urinary symptoms. In other cases there are at first the ordinary urinary symptoms, but these disappear spontaneously. According to White the condition occurs in 10 per cent of cases of renal tuberculosis coming to operation, but the autopsy figures may be nearly twice as high.

The final stage is one in which the kidney becomes a functionless mass of tuberculous tissue. The kidney may be enlarged from pyonephrosis.

or may be shrunken and atrophic. The ureter is occluded. Lime salts are deposited in the caseous mass, and extensive calcification may occur.

Microscopically the picture depends entirely on the stage of the disease. The early lesion presents the characteristic appearance of a miliary tubercle. As the disease advances the unaffected part of the kidney may show a condition of toxic tuberculous nephritis, due to the action of the tuberculous toxins on the renal epithelium. In the late stages amorphous areas of caseous material are surrounded by tissue which has become so fibrosed that all resemblance to kidney structure is lost.

Fig. 248.—Tuberculous pyonephrosis with marked involvement of the ureter.

Healing.—There is still much difference of opinion as to whether a tuberculous kidney can undergo healing. Some of the clinical evidence is in favor of it, but in the postmortem room no example of healed tuberculosis of the chronic ulcerative type, that is to say of renal phthisis, has ever been seen. To the writer it appears that the matter, which is one of great clinical importance, is one of degree. When renal phthisis has developed it is unreasonable to expect that healing should take place, although even here a partial form of healing may occur through exclusion of the tuberculous focus by a ring of fibrous tissue, giving rise to the condition known as closed renal tuberculosis, in which the process becomes quiescent though still potentially active and capable of mischief. But tuberculosis

does not start as renal phthisis but as a minute lesion which may, never-theless, be associated with the presence of bacilli in the urine. There is no reason why such a lesion should not heal. It would leave a scar so minute that it could not be detected, or if discovered it would not be possible to determine its nature. Medlar has demonstrated healed renal lesions in experimental tuberculosis, but these lesions have not communicated with the renal pelvis.

The probable truth would appear to be that early lesions with bacilluria may heal if the patient is placed under sanatorium conditions. The mere fact that tubercle bacilli are coming from a kidney therefore is no justi-fication for removing it. On the other hand there is no chance that a well developed renal phthisis with destruction of the kidney will heal, so that surgical removal is the only hope.

The Other Kidney.—Renal tuberculosis is at first a unilateral condi-tion. Sooner or later, however, it is most likely to become bilateral. Two different pathological conditions may occur in the other kidney: (1) toxic nephritis of tuberculous origin; (2) renal tuberculosis.

The toxic nephritis is due to absorption of toxins from the infected kidney. It manifests itself by the appearance of albumin and it may be of casts in the urine. When the primary source of infection is removed this nephritis speedily clears up.

Tuberculous infection may pass down the ureter from the first kidney, infect the bladder, and pass up the other ureter to infect the second kid-ney. Or the infection may be hematogenous in origin. The tuberculous toxic nephritis just alluded to weakens the resistance of the kidney, and it succumbs to a blood-borne infection. Which of these methods of in-fection is the commoner it is difficult to say.

The unilateral character of early tuberculosis is well exemplified in the case of a horse-shoe kidney. In this condition there may be widespread infection of one pelvis and yet the other may be quite free. Microscopic examination, however, will frequently reveal the presence of miliary tubercles in the cortex of the other half. These, apparently, are due to infection carried by the lymphatics in the capsule.

The *prognosis* naturally depends largely on the condition of the good kidney. If there is no pus in a catheter specimen of urine from that kidney there is over 40 per cent chance of a five-year cure (Emmett and Kibler). If guinea-pig inoculation is negative the outlook is still better. If there is pus from the good kidney the prognosis is poor. Even in cases of bilateral renal tuberculosis, however, some patients live for a considerable number of years without operation.

Ureter and Bladder.—Tuberculosis of the ureter and bladder is always secondary to tuberculosis of the kidney. It shares in common with other secondary lesions the characteristic that when the primary source is re-moved the secondary lesion rapidly clears up provided that the disease is not too far advanced.

In the *ureter* the infection passes down in the submucosa. In this layer there may be definite tubercles, or the formation of a diffuse, tuberculous granulation tissue, such as is found in the intestinal submucosa. Ulceration of the mucosa occurs, followed by infiltration and thickening of the muscu-lar and serous coats. The upper and lower thirds are usually much more

involved than the middle third. Scar formation may give rise to stricture, but more often the ureter is converted into a rigid, thickened, and markedly dilated tube.

In the *bladder* infection commences at the opening of the ureter, and spreads along the submucosa of the trigone, giving rise to ulceration of the overlying mucous membrane. As involvement of the ureteric opening occurs comparatively early in renal tuberculosis, cystoscopic examination plays a most important part in the diagnosis of the condition. In the earliest stage there is an irregular area of hyperemia and swelling surrounding the ureteric opening. Later the mucosa becomes thickened and infiltrated, and groups of tubercles or vesicles may be seen. The ureter may appear as a thickened ridge traversing the wall of the bladder, and the opening may project like a crater into the bladder. In chronic cases the opening becomes funnel-shaped (golf hole ureter). Ulceration of varying extent develops sooner or later. Even before removal of the kidney many of the bladder lesions show a remarkable tendency to heal, so that healed tubercles may be found in the neighborhood of quite active lesions. Removal of the kidney may be followed by complete recovery.

RENAL CALCULUS

It is convenient in this place to consider the general problem of urinary calculi, whether in the kidney, the ureter, or the bladder. The special characteristics of the various calculi will be described under the heading of the various organs in which they occur.

A urinary calculus is a stone-like body composed of urinary salts bound together by a colloid matrix of organic matter.

It consists of a nucleus around which are deposited concentric layers of one or more of the urinary salts. These salts as they occur in the urine are of crystalline structure. In a calculus, however, the crystalline structure is entirely lost, and all that can be seen is an amorphous mass of granules embedded in an albuminoid matrix. The albuminous material, therefore, occurs not only in the nucleus but in all the successive layers which go to make up the calculus.

Three principal constituents go to the making up of urinary stones: uric acid, calcium oxalate, and ammonio-magnesium phosphate—the so-called triple phosphate. These may occur alone, but frequently they are combined. The X-ray visibility of the stone depends on its atomic weight.

Stones have been divided into two groups, primary and secondary.

Primary stone forms in the urine without any antecedent inflammation. It consists usually of uric acid, urates, or calcium oxalate, although in rare cases it may be composed of cystin, xanthin, or calcium carbonate. The urine is acid.

Secondary stone is formed as the result of inflammation. The common constituent is ammonio-magnesium phosphate, but amorphous phosphates and ammonium urate may enter into its composition. The urine is alkaline.

The uric acid stone may occur alone, but is usually combined with urates and oxalates. The stone is of moderate hardness, light to dark

brown in color, and on section when polished it displays the wavy concentric markings of an agate. It occurs in acid urine.

The oxalate stone may be recognized by its extreme hardness, its dark color due to staining with blood from the injuries it produces, and its peculiarly spiny and prickly exterior, from which it derives its name of mulberry calculus (Fig. 249). On section it shows wavy concentric laminae. It occurs in acid urine.

The phosphatic stone, consisting of triple phosphates, may occur pure, or as a covering of a primary stone. It is white, smooth, soft, and friable (Fig. 250). When mixed with other constituents, however, it may be tinged with their color. It occurs in alkaline urine.

Etiology.—The conditions which govern the formation of urinary calculi are still far from understood. The two factors which naturally suggest themselves are a high concentration of crystalline salts in the urine and inflammation in the

Fig. 249.—Two examples of oxalate calculi.
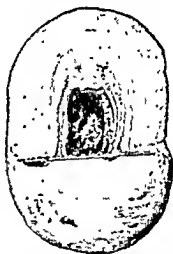
Fig. 250.—Phosphatic calculus removed from bladder. The nucleus is formed of the ova of a nematode worm.

urinary tract. But the urine may be loaded with crystals for long periods without the formation of stone. Secondary phosphatic calculi in the bladder it is true are a not infrequent accompaniment of the cystitis associated with enlargement of the prostate, but on the other hand inflammatory conditions of the renal pelvis are very common, whereas renal stones are comparatively rare. Moreover pyelitis is much commoner in women than in men, whereas the incidence of renal stone is just the reverse.

In spite of these facts there is evidence that *infection* and a *high urinary concentration of salts* are factors which cannot be disregarded. Rosenow and Meisser, working with streptococci from the urine of pa-

tients with multiple recurrent calculi, have succeeded in repeatedly producing calculi in the kidneys of dogs by implanting these streptococci in devitalized teeth of the dogs, thus establishing foci of chronic infection. Keyser has obtained equally interesting results by feeding rabbits with oxamide, a diamide of oxalic acid. In 50 per cent of these rabbits there was definite stone formation. The subcutaneous injection of butyl oxalate, an ester of oxalic acid, was accompanied by an intense oxaluria for a considerable time, and by the formation of definite oxalic acid calculi.

The fusing of urinary crystals into non-crystalline calculi appears to depend on the *colloid content of the urine*. It is probable that the colloids of the urine normally keep the water-insoluble crystals such as urates and oxalates from crystallizing out. The presence of an abnormal colloid or an interference with the normal colloids of the urine may cause the normal crystalloids to be precipitated; an undue concentration of crystalloids may under certain circumstances produce the same results. It would appear, however, that not every inflammatory colloid is sufficient to bring about the precipitation, for, as already remarked, pyelitis is very frequently present without any stone formation. It may be, as Rosenow suggests, that certain specific bacteria may be required for the production of stone-forming colloid. It is well known that certain patients have what may be called a stone-forming diathesis; stone after stone may be removed from the kidney, but it continues to produce new ones.

These latter cases may be associated with an increased calcium content of the blood, the most important cause of which is hyperparathyroidism. As a result of overactivity of the parathyroids the bones become decalcified, and the calcium removed from them first floods the blood and is then deposited either in the renal tubules or in the renal pelvis, giving rise to the formation of a calculus in the latter position.

The *absence of vitamin A* from the food tends to induce stone formation in animals. This may be because there is a greater tendency to infection, or the lack of vitamin may bring about a change in the colloid and therefore precipitation of the crystalloids. The *geographical distribution* of stone has probably a dietary basis. It is common in parts of India and Egypt, but comparatively rare in North America. A hundred years ago stone formation was common in European children; now it is rare, probably owing to the improvement in diet.

There can be no doubt that the reaction of the urine has a very important bearing on the type of stone found. A stone may show several layers of uric acid followed by deposits of phosphates. The change is due to an alteration in the reaction of the urine caused by infection with pyogenic cocci which are ammoniogenic. Subsequent infection by the Bacillus coli may bring back the urine to acid, with the deposition of calcium oxalate.

The concentric ring formation is probably due to the phenomenon of "rhythmic precipitation," which is the cause of the concentric rings in many geological substances such as the agate. When a solution of a salt is brought in contact with a colloidal gel it is precipitated in a series of rings (Liesegang rings) instead of in a uniform manner.

To sum up: The precipitation of the crystalloids from the urine depends on their concentration and on their relation to normal and abnormal colloids. The latter are not only concerned with the precipitation, but

also bind the crystalloids together into a non-crystalloid mass. The colloid disturbance is probably dependent on infection, and perhaps in some cases on deficiency of vitamin A.

Stone in the Kidney.—A stone in the kidney is formed in the renal pelvis. It may remain in the kidney, or may, before it has become too large, pass down into the ureter where it forms a ureteral calculus, or finally it may reach the bladder where it becomes a vesical calculus. Most stones in the bladder originate in the kidney. The condition is much commoner in men than in women. It usually occurs between the ages of twenty and forty. The stone as a rule is single, but occasionally numerous small stones may be found (Fig. 252).

Randall has described what he calls initiating lesions of a calculus. While small stones under the hand lens show a crystalline structure on one side, on the other they present a facet indicating attachment to some tissue. At autopsy a "milk patch" may sometimes be seen on a papilla, usually less than 2 mm. in diameter. This corresponds with a deposit of calcium in the cells lining the tubules which are necrotic (Fig. 251). Presently the epithelial covering is lost and a tiny black dot is seen on the milk patch. On this basis a secondary crystalline deposit, the true stone, is formed, which tends to undermine the patch so that the latter is finally torn away. This secondary deposit of calcium salts comes from the urine in the calyx.

A renal calculus is usually uric acid or oxalate in type. The effects produced in the kidney are so variable that they cannot be described in detail. They are dependent on three factors, retention, infection and suppuration. The symptoms depend mainly on the size of the stone. As Cabot puts it, "little stones, like little dogs, are likely to make the most noise." The large stone is often a silent stone.

Fig. 251.—Randall's patch, showing deposit of calcium in renal papilla. × 50.

(1) If the stone produces obstruction of the ureter and retention, a condition of hydronephrosis is superadded to that of stone. The stone may or may not completely fill the dilated pelvis. In the latter case the stone is usually of the branching or coralline variety. Should the obstruction be complete, calculus anuria will develop, with atrophy of the kidney.

(2) In many cases infection develops as the result of the stone in the kidney. The bacteria probably reach the kidney through the blood stream. The effect depends on the condition of the kidney at the time. If there is little or no obstruction the result will be a pyelonephritis. If, however, dilatation has already occurred a condition of pyonephrosis will develop. The infection will naturally hasten the formation of the stone.

(3) Wherever the stone presses on the kidney ulceration will occur. In the case of a large stone the effect will be extensive destruction of kidney tissues. In rare cases the stone may ulcerate through the wall of the pelvis or ureter and escape into the abdominal cavity.

Stone in the Ureter.—At any moment a small stone may leave the kidney and enter the ureter. It may traverse the canal and enter the
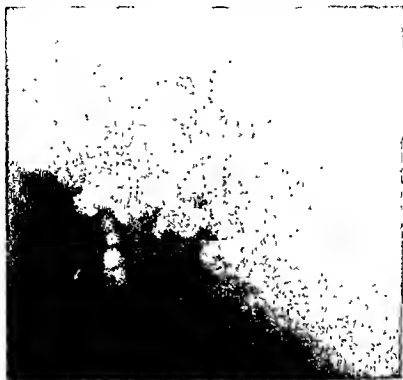
Fig. 252.—Multiple calculi in renal pelvis. These stones formed in less than a month.

bladder, giving rise to the agony of renal colic. Or it may be arrested in the ureter and lodge there. At the point of arrest the wall of the ureter becomes ulcerated, and later a stricture may develop. The ureter above the obstruction becomes greatly dilated. X-ray studies have shown that ureteral calculus is a much commoner condition than was formerly suspected. Indeed some observers state that ureteral stone is almost twice as common as stone in the kidney.

HYDRONEPHROSIS

Hydronephrosis is a condition of dilatation of the renal pelvis and calyces, with accompanying destruction of the kidney parenchyma (Fig. 253). It is caused by obstruction to the outflow of urine. Until recently it was believed that this obstruction might be either organic or functional, but the idea of a functional obstruction at the pelvi-ureteric junction due to overaction of the sympathetic system has now been abandoned. A similar fate has befallen the various operations on the sympathetic designed to relieve this condition.

The obstruction may be congenital or acquired. *Congenital* obstruction takes the form of valve-like folds of the mucosa which are present in the fetus and sometimes at birth, or definite constrictions. These lesions, which are readily overlooked by the pathologist unless searched for with particular care, are commonest at the uretero-pelvic junction, but also occur at the pelvic brim and in the intravesical portion of the ureter. The most extreme cases of hydronephrosis belong to this group, because the condition is symptomless until it becomes far advanced.

In acquired obstruction the lesion may be in the urethra, the bladder, and the ureter. (1) In the *urethra* the usual causes are stricture and enlargement of the prostate. In children (boys) there may be a fold across the membranous urethra causing a congenital form of hydronephrosis. In all of these the hydronephrosis is bilateral, although often more marked on one side than the other, and is accompanied by hydro-ureter. (2) In the *bladder* a calculus acting as a ball valve may produce intermittent obstruction. Or the internal sphincter may be unable to open owing to neuromuscular dysfunction, as in tabes dorsalis and injury to the cord. Here again the condition is bilateral. (3) In the *ureter* the obstruction is likely to be at the upper end (pelvi-ureteric junction) or the lower end (ureterovesical junction). A renal calculus at the upper end or a ureteral calculus at the lower end may cause obstruction. As the result of raised intravesical pressure there may be marked pressure on the ureters as they pass obliquely through the muscular wall of the bladder. It often happens, therefore, that the ureters are of normal size at their *openings into the bladder although greatly* dilated through the rest of their course. In the wall of the ureter there may be a stricture, either inflammatory or tuberculous in nature. Such a stricture is usually at the pelvi-ureteric junction. Pressure on the ureter from without may cause obstruction. An accessory renal

Fig. 253.—Hydronephrosis and dilatation of ureter due to impaction of stone at lower end of ureter.

artery, *i. e.*, an aberrant branch arising at a lower level, may be found in contact with the dilated pelvis at the pelvi-ureteric junction, and may appear to be causing pressure. This used to be regarded as a common cause of hydronephrosis, but it is now thought more probable that the dilatation usually occurs before the pressure. A movable kidney may cause kinking of the ureter, but is seldom a cause of hydronephrosis. Congenital folds across the upper end of the ureter may cause the condi-

tion in children. In all of these cases the hydronephrosis is unilateral. Symptoms are much more likely to be marked in right sided cases than in those on the left side. The latter are often remarkably silent.

A combination of renal ischemia and back pressure is particularly liable to produce hydronephrosis. This is well illustrated by the experimental work of Hinman and Hepler. They ligated the posterior branch of the renal artery, thereby causing infarction and throwing out of function more than one-third of the kidney. When this is combined with total ureteral obstruction, enormous sacculation of the infarcted area is produced in a very short time, owing to lessened resistance of the degenerated parenchyma to urinary back pressure.

Morbid Anatomy.—The essential change in hydronephrosis is dilatation of the renal pelvis or calyces. The normal pelvis has an average capacity of 7 to 10 c.c. The dilatation may become so enormous that the hydronephrotic sac occupies the entire abdominal cavity, and one case is reported in which there were 36,000 c.c. The cases showing very great dilatation are nearly always those in which no obstruction is found (idiopathic group).

Three types may be recognized, although the dividing line may not be well marked: (1) renal, (2) pelvirenal, (3) pelvic. In the *renal* type the pelvis escapes, but the calyces are dilated and the kidney destroyed owing to the presence of a calculus. The pelvirenal type is perhaps the most common form, in which both the pelvis and the kidney are equally involved. It is caused by organic obstruction at the pelvi-ureteric junction. The *pelvic* type is the idiopathic form, in which the pelvis is mainly or solely involved. As already mentioned, this is the type in which the greatest dilatation is likely to occur. When the hydronephrosis is due to a stone at the upper end of the ureter, there is sure to be accompanying inflammation, and the fibrosed and thickened pelvis is unable to dilate to the same extent. The principle is the same as that which governs Courvoisier's law regarding the effect of obstruction on the gall bladder.

The effect of sudden complete obstruction differs in degree but not in kind from that produced by gradual partial obstruction. It is a mistake to think that ligation of the ureter causes anuria followed by atrophy. The effect is hydronephrosis followed by hydronephrotic atrophy without symptoms. The dilatation following complete obstruction comes on more quickly, but never reaches the extreme grade that is seen in partial obstruction, whether organic or functional.

In the process of dilatation first the pyramids and then the cortex suffer, until finally the kidney becomes converted into a huge lobulated bag of fluid in which only vestiges of the interlobular septa remain. The cortex is thinned to a mere shell. The fluid is clear and watery, and its content of urea, uric acid, and salts is very low. Should infection occur the condition changes to one of pyonephrosis or infected hydronephrosis.

Microscopically the striking feature is great atrophy of the tubules while the glomeruli remain comparatively intact. This dissociation is peculiar to hydronephrosis. In the late stages the glomeruli also become fibrosed, and the end picture is that of chronic nephritis or nephrosclerosis, although even when the sclerosis is extreme areas containing normal glomeruli still persist.

The *fluid* in the hydronephrotic sac does not become stagnant, but remains fresh. The reason for this is that there is constant absorption of fluid and secretion of fresh fluid. It used to be thought that absorption took place into the veins by a "pyelovenous back-flow" (Hinman and Lee-Brown), but although this can be demonstrated in animals when the pressure in the renal pelvis is suddenly increased, it is probable that in man absorption is by way of the renal tubules.

The condition of the *other kidney* in unilateral cases is of importance. It can be shown experimentally that after the ureter has been obstructed for three weeks the other kidney hypertrophies and assumes *additional* function. It not only assumes it but retains it, so that the obstructed kidney atrophies through lack of stimulus. It is said that obstruction for more than three weeks spells disaster to the function of the kidney, even though the obstruction be then removed.

TUMORS OF THE KIDNEY

The study of kidney tumors is one of the most perplexing and confusing chapters in the whole of pathology. The history of the various conceptions which have been popular at different times is full of interest, but the reader must be referred to the pages of Ewing for a full discussion of the subject. A large number of different varieties have been described, but the grounds for considering many of these as distinct forms of neoplasm appear insufficient to the writer, and at the risk of erring too far in the opposite direction only two types will be recognized. These are the hypernephroma or Grawitz' tumor and the embryoma or Wilms' tumor. It will be found that the vast majority of tumors encountered in actual practice can be placed in *one* or other of these groups.

Hypernephroma.—It was in 1883 that Grawitz pointed out the close resemblance between the common yellowish kidney tumors which were then regarded as lipomas and the hyperplasia of the adrenal cortex first described by Virchow. Moreover he demonstrated the occasional presence of adrenal remnants or "rests" in the capsule and cortex of the kidney. From these facts he concluded that the fatty tumors were adrenal in origin, being derived from the adrenal or hypernephros rests in the kidney. The tumor was therefore known as a hypernephroma or Grawitz' tumor. This conception, which soon became popular, was attacked ten years later by Sudeck, followed by many others, who maintained that these tumors arose from the cells of the renal tubules, and were to be regarded as renal carcinomas. The controversy has never been settled. Young considers that it is so far from being settled that the name of hypernephroma should be discarded, as there is no real proof that the tumor arises from adrenal tissue, and that the term nephroma should be substituted. This, however, would include the entirely different embryomas, which is out of the question.

In the first edition of this work two tumors were described, following the example of Ewing and other writers. These are the hypernephroma and the renal carcinoma. I feel now that little is to be gained from this distinction. The differences between the tumors, both gross and histological, are no greater than the differences between various parts of one tumor. We shall therefore consider all of these tumors under the well

established heading of hypernephroma, with the clear understanding, however, that the use of this name does not commit one to the adrenal theory of origin of these tumors. They are probably renal carcinomas. In favor of the renal origin of these tumors the following points may be mentioned. Clear, lipoid-filled cells are present in adenomas of the kidney composed of typical tubules and certainly not of adrenal origin. The hypernephroma may show a tubular structure, never seen in the adrenal cortex or in tumors of adrenal cortex. Adrenal cortical tumors are associated with sex disturbances (virilism); hypernephroma never is.

Gross Appearance. — The tumor forms a large, rounded, encapsulated mass, which usually does not cause much change in the shape of the kidney. It is rather commoner in the upper pole but is quite often found in the lower pole, and more seldom in other parts of the kidney. The two chief characteristics of the cut surface are the yellow color and the remarkably variegated appearance (Fig. 254). Darker areas of hemorrhage are very common, and cysts of varying size are often numerous (Fig. 255). Some of these are true cysts and contain a clear serous or jelly-like material, others are the result of degeneration and contain blood. In the early stages at least a central fibrous core can often be distinguished from a more cellular cortical part.

At first the growth is sharply separated from the kidney by a definite fibrous capsule, but sooner or later the capsule gives way and true invasion of the kidney occurs. There is a special tendency to vascular involvement, invasion of the renal vein and even the inferior vena cava occurs, and widespread metastases are the result. The lungs and the long bones are the principal sufferers. In the X-ray picture of the lung the secondary growths often present a peculiarly clear-cut, circumscribed outline, a "cannon ball appearance," which is so characteristic that a diagnosis can be made by the roentgenologist (Fig. 256). This tumor is one of the most common causes of secondary tumors in bone, together with carcinoma of the breast, the prostate, and the thyroid. A spontaneous fracture may be the first indication of a growth in the kidney. The secondary growth usually closely resembles

Fig. 254.—Hypernephroma. The variegated character of the cut surface is well seen.
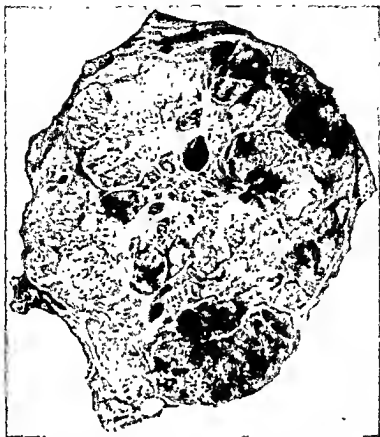
Fig. 255.—Hypernephroma. The variegated appearance, the hemorrhagic areas, and the cyst formation are well shown.

Fig. 256.—Hypernephroma. Two large secondaries in the lung

the primary one, so that a diagnosis of hypernephroma may sometimes be made from an examination of the bone lesion. Not infrequently the metastasis is single, so that excision may be possible. Tumors arising in the adrenal cortex do not display this tendency. The peculiar sex changes, so characteristic of growths of the adrenal, never occur in renal hypernephroma. This tumor has a well marked tendency to invade and obstruct the pelvis, and may therefore be confused with a true tumor of the renal pelvis. The outline of the pelvis is often distorted, a deformity which can be detected in a pyelogram.

Microscopic Appearance.—The picture varies considerably in different specimens and in different parts of the same specimen. The cells are highly characteristic. They are of large size, and the cytoplasm is peculiarly clear, or slightly granular so as to give it a foamy appearance (Fig. 257). This is due to the presence of a large number of lipoid globules,

Fig. 257.—Hypernephroma. The cells have a characteristically clear cystoplasm. × 325

an ester of cholesterol, which in frozen sections can be stained with Scharlach R, but in paraffin sections is dissolved out. It is true that this lipoid, which is doubly refractive to polarized light, is also characteristic of the adrenal cortex, but this does not prove the adrenal origin of the tumor, for some of the renal cells contain the same material normally and under pathological conditions (nephritis and nephrosis) they may be loaded with it. The large clear cells are not pathognomonic of hypernephroma, but are associated in some way with the kidney. They are seen in the normal cat's kidney. Inflammation increases the lipoid content of the renal cells, and clear cells are found in inflammatory conditions of the kidney. As Hugh Young remarks, the resemblance to adrenal cells is merely accidental.

The arrangement of the cells is very variable. Usually they are arranged in sheets or cords, which may reproduce the structure of the adrenal cortex

with tolerable fidelity. Or they may present an alveolar or tubular arrangement, which indicates very strongly their renal origin. It is these which are classed as renal adenocarcinomas. There may be a well marked papillary arrangement, the papillary processes projecting into the lumen of the tubular spaces. It is of extreme importance to note, however, that in one part of the tumor the structure may suggest with equal force a renal origin. It is for this reason that the two groups have been combined in this discussion. The stroma is scanty, but the blood vessels are numerous and often very large, thus accounting for the frequent hemorrhages into the tumor.

The *symptoms* are urinary rather than general. Hematuria is the cardinal symptom. Hypernephroma is one of the four serious conditions which cause hematuria, namely tumor of the kidney, tumor of the bladder, tuberculosis, and stone. Pain (apart from renal colic) is only present in about one-third of the cases. The tumor can only be felt late in the disease. As Israels pointed out long ago, these tumors are sometimes
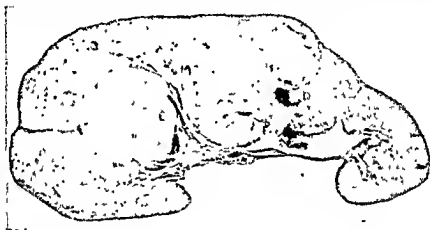
Fig. 258.—Embryoma of kidney, showing uniform nature of cut surface.

associated with remarkable disturbances of temperature. In one of my cases the two chief features of the illness were the presence of a lesion in the lung (confirmed by X-ray) and an almost continuous fever over a period of 12 months. A tumor of the kidney was never suspected till shortly before death, although the case was most carefully studied. Autopsy revealed a small hypernephroma with a secondary growth in the lung.

Embryoma. Wilms' Tumor.—In the older writings the tumors of childhood were classed as sarcomas, although they showed great variations in structure. Recent work has thrown entirely new light on the subject, and most of these tumors are now regarded as of embryonal type, although other varieties of neoplasm may also occur.

The greatest frequency is between the first and third years, and after the age of five these growths are infrequent, although they may also be met with in adults. There is a curious tendency in children for these tumors to be bilateral, a tendency which, as Bland-Sutton has pointed out, is shared by paired organs such as the ovaries, testes, eyes, and crura cerebri.

Gross Appearance.—They vary greatly in size, being sometimes quite small, but often reaching extraordinary dimensions. Bland-Sutton mentions one case in which the tumor weighed 31 pounds. The growth may commence in the substance of the kidney, usually at one or other pole, or it may apparently start in the pelvis. Rapid increase in size is the rule, but the ureter is not invaded until later in the disease, which may account for the customary absence of pain and hematuria. The consistence is soft, the color grey or yellowish. The cut surface is comparatively uniform, in marked contrast to the variegated appearance of the Grawitz' tumor (Fig. 258).

The tumor spreads by invasion of the kidney, or later of the neighboring organs such as the liver, spleen, and intestine. Metastases by the blood stream are not frequent, but may occur.
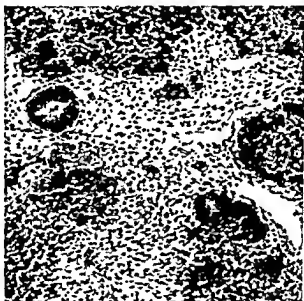
Fig. 259.—Wilms' tumor. Both the carcinomatous and sarcomatous characters are apparent. × 150.

Microscopically the appearance is so varied that a detailed description is impossible. It may be sarcomatous in type, round-celled, spindle-celled, or adeno-sarcomatous. More common, however, is the "mixed" tumor (Fig. 259). This variety consists of an undifferentiated cellular stroma in which may be found tubules, smooth muscle, striated muscle (rhabdomyoma), cartilage, bone, and fat. The tubules bear no resemblance to normal kidney tubules.

The embryonal tumors of the kidney are of developmental origin. The kidney is an epithelial organ, but it is mesodermal in origin, arising from the intermediate cell mass. If sections of a developing kidney are examined the convoluted tubules are seen to develop from undifferentiated cellular connective tissue. As this is just the appearance presented by Wilms' tumor, the condition may be regarded as a continuation of an early stage of development. The muscle and cartilage may be regarded as perversion of mesodermal growth.

The *clinical picture* differs markedly from that of hypernephroma, for urinary symptoms are usually absent and there is no pain until the tumor has attained a large size. The principal feature is the tumor, which of course is more readily detected in the child than in the adult. The duration is usually only a matter of a few months.

Many other varieties of tumor have been reported as occurring in the kidney. These will be found described in textbooks of pathology, but the general design of this book does not warrant a detailed discussion of them here.

Small nodules causing no symptoms may be found at autopsy, *fibromas*, chiefly in the pyramids and papillae, *adenomas*, chiefly in the cortex. *Angioma*, a rare tumor usually occurring in the renal pelvis, sometimes in the pyramid and even in the cortex, may cause sudden severe hematuria. True *sarcomas*, round-celled or spindle-celled, probably always arise in the capsule, from which they invade the kidney. *Carcinoma*, adenocarcinomatous in type, has been reported.

TUMORS OF THE RENAL PELVIS AND URETER

These tumors are so rare that they merely deserve a passing mention. They closely resemble tumors of the bladder, and may therefore be in

Fig. 260.—Carcinoma of renal pelvis causing hydronephrosis.

their order of frequency: 1. simple papilloma; 2. malignant papilloma; 3. squamous-celled carcinoma.

The renal pelvis is the common site of origin, but in exceptional cases the growth may commence in the ureter. The tumors are usually multiple, and the wall of the pelvis may be covered with masses of finely branched villous processes (Fig. 260). These are very friable, and as they are extremely vascular hemorrhage readily occurs. In many instances the condition is associated with renal calculus, and cases have been reported in which a tumor has developed after exploratory incision of the pelvis. Irritation thus appears to play a part of some importance in the etiology.

The tumor tends to grow along the lumen of the ureter, with resulting blocking or hydronephrosis. In the case of the malignant growths particles of tumor tissue may be carried down and implanted on the bladder wall. The second and third varieties are of great malignancy, and secondary growths are set up at an early date not only in neighboring lymphatic glands but in distant organs. The development of squamous-celled carcinoma in a transitional epithelium is to be explained by a metaplasia, the result probably of chronic irritation, which transforms the transitional epithelium of the renal pelvis into a squamous-celled epithelium.

PERIRENAL TUMORS

These extremely rare tumors are of considerable variety, but they all arise from the fibrous or fatty capsule of the kidney. The commonest form is the *lipoma*, which may contain so much fibrous tissue as to deserve the name fibro-lipoma. These tumors may attain an enormous size.

Next in frequency come fibromas and then sarcomas and "mixed tumors," supposed to arise from remnants of the Wolffian body.

Invasion of the kidney practically never occurs so that renal symptoms are absent. This is a point of great importance in the differential diagnosis, but there are so many conditions with which a perirenal tumor may be confused that a correct diagnosis is seldom made.

TUMORS OF THE ADRENAL

Although the adrenal glands have no connection with the urinary tract, it is convenient to consider the subject of adrenal tumors in this place.

The adrenal gland, like the pituitary, consists of two parts which are different in origin, of different physiological function, and present different pathological conditions. The cortex is of mesoblastic origin, yet the tumors which arise from it are of an adenomatous or epitheliomatous character. The medulla is derived from the sympathetic nervous system, and the tumors to which it is liable are nerve cell tumors. The behavior of the two sets of growths is entirely different.

Tumors of Adrenal Cortex.—At autopsy a small nodule is sometimes discovered, light yellow in color, and seldom larger than a pea in size, a condition which Virchow originally named struma suprarenalis. These masses consist of normal adrenal tissue, and should be regarded as a nodular hyperplasia rather than a neoplasm.

A *diffuse hyperplasia* of the cortex sometimes occurs, as a result of

which the adrenal may become as large as the kidney. In the female these tumors are often associated with masculine changes which, in conjunction with a mass in the kidney region, are quite pathognomonic.

Adenoma of the cortex is similar to the nodular form of hyperplasia, but the arrangement of the cells is more atypical and neoplastic. Irregular lumina are frequently seen. As a rule they remain quite small.

Carcinoma, also called adrenal hypernephroma, is the most frequent variety of adrenal tumor. The cases reported as sarcoma are probably' of epithelial origin. The tumor usually occurs about middle life. It may attain a large size, and is soft, of a yellow color, and prone to hemorrhage. *Microscopically* the cells may attempt to reproduce the acini of the zona glomerulosa or the columns of the zona fasciculata. In other cases the arrangement is wilder, and no adrenal structure can be recognized. The cells may show a decided perivascular arrangement. Giant cells are sometimes very numerous.

The tumor is very malignant, and *metastases* occur at an early date. There is local extension to the kidney, and the adrenal may completely disappear. The adrenal and renal veins are invaded, as in hypernephroma. Spread takes place both by the blood stream and the lymphatics. The metastases are widespread, but the organs most frequently involved are the liver, lungs, and brain. The opposite adrenal is often affected. The retroperitoneal, mesenteric, and mediastinal glands are enlarged. Contrary to the usual opinion the bones are seldom the seat of metastatic deposits, only in one out of 48 cases collected by Hartmann and Lecene, whereas the liver was involved in 23 cases. Bone metastases are almost always due to growths which arise in the kidney and not in the adrenal.

The *symptoms* are similar to those of Cushing's syndrome. Indeed it is probable that the basic lesion of that syndrome is in the adrenal cortex and not a basophil adenoma of the pituitary as was formerly believed. In children there is precocious sexual development of the sexual organs with an intensification of maleness, a condition known as adrenal virilism. In girls there is marked development of both primary and secondary male characters, including hypertrophy of the clitoris and hirsutism. In women there is amenorrhoea, atrophy of uterus and breasts, hirsutism, and a general tendency to maleness. All of these features disappear with removal of the tumor. A good index of androgenic activity is afforded by the 17-ketosteroid test on the urine. The normal figure is from 10 to 20 mgm. 17-ketosteroids per twenty-four hours in the male and 5 to 15 mgm. in the female. In cases of adrenal cortical tumor the figure is usually over 200 mgm. in twenty-four hours.

Tumors of Adrenal Medulla.—The adrenal medulla consists of nerve cells and chromaffin cells (pheochromocytes). Three types of tumor may occur: (1) *neuroblastoma,* arising from primitive neuroblasts; (2) *ganglioneuroma,* arising from mature nerve ganglion cells; (3) *pheochromocytoma,* arising from chromaffin cells. Of these the neuroblastoma is by far the most important by reason of its malignancy.

Neuroblastoma.—The tumor is confined to children, usually under four years of age. It is often bilateral. Rarely it may arise from sympathetic nerve tissue in the abdomen or thorax. The tumor is soft, rapidly growing, and may attain a great size. Microscopically it is composed of

small round cells, so that it used to be regarded as a sarcoma before these cells were recognized as neuroblasts. The characteristic feature is the presence of small rounded masses known as rosettes (Fig. 262), which consist of a center of neurofibrils surrounded by cells. Neurofibrils are also scattered amongst the cells.

The *spread* of the tumor is noteworthy. It has a special predilection for the bones of the skull, particularly the orbit, so that proptosis may be a striking feature, but metastases may also be found in the sternum, ribs, and long bones (Fig. 261). Greig has shown that the cephalic metastases may be in the soft parts with secondary invasion of the bone, rather than in the cranium itself. There is a very characteristic periosteal reaction, with the formation of fine spicules of bone which can be recognized in the X-ray picture. The form with bone metastases has been called the Hutchi-
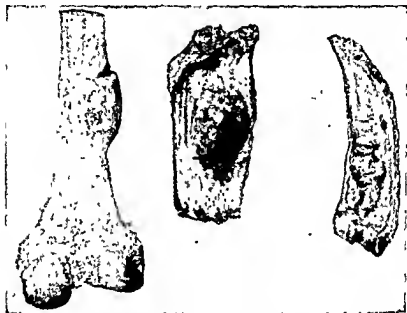
Fig. 261.—Metastatic neuroblastoma in femur and ribs; primary tumor in adrenal medulla.

son type. In other cases spread takes place principally to the liver, and that organ may be enormously enlarged. This is known as the Pepper type. As the types may be mixed, these terms might well be discarded. Secondary growths are occasionally found in other organs. The first local evidence of disease may be the appearance of an ecchymotic spot round one eye, which the mother usually attributes to a fall. To the physician it may suggest chloroma or scorbutus. At the same time as the appearance of the hemorrhage or a little later proptosis is noticed, and soon a large orbital tumor develops. If the abdomen be now examined a tumor will usually be felt. In a few cases it cannot be detected until a later date.

The Pepper type of tumor is less well differentiated, runs a more rapid course, and kills the child before the growth in the adrenal has had time to attain any considerable size. The Hutchison type is better differ-

entiated and shows well formed rosettes, it grows more slowly, and the adrenal tumor may be so large that it can easily be detected clinically.

Pathology.—It was Marchand who, in 1891, first suggested that tumors of the adrenal medulla might represent a reproduction of the anlage of the sympathetic nervous system, and the work of J. H. Wright in 1910 has placed this idea on a sure foundation. These tumors, so frequently described as round-cell sarcomas or lymphosarcomas, are really nerve cell tumors, neurocytomas or neuroblastomas. Indeed it is now regarded as probable that most of the retroperitoneal round-cell sarcomas of infants are of this character, and similar growths have been described in connection with the cervical, thoracic, and peripheral nervous systems.
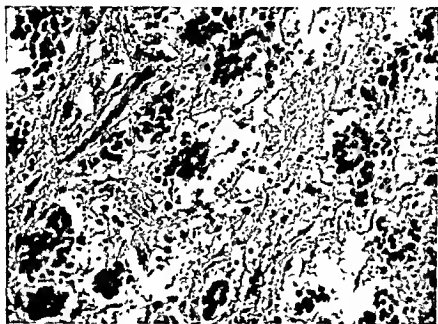
Fig. 262.—Neuroblastoma of the adrenal. Several rosettes are scattered through the section. × 250.

Ewing describes one such tumor which appeared to originate in the femoral sympathetic plexus below Poupart's ligament.

In the *microscopic* picture there are large numbers of round cells like the cells of a sarcoma, fibrils of varying degree of distinctness, and imperfect ganglion cells. The fibrils, which take on a brown color with van Gieson's stain, are arranged either in longitudinal bundles or as little compact balls round which the cells are grouped to form "rosettes" (Fig. 262). Such rosettes are seen in the sympathetic anlage from which the adrenal is developed, and they may give rise both to ganglion cells and chromaffine cells. The metastases are composed mainly of round cells, but rosettes and rudimentary ganglion cells have also been described.

CYSTS OF THE KIDNEY

There are three main varieties of cysts of the kidney: 1. multiple serous cysts; 2. polycystic kidney; 3. solitary cyst.

Hydatid cysts and dermoid cysts are pathological curiosities which may be mentioned in passing.

1. **Multiple Serous Cysts.**—These are small cysts found in both kidneys in chronic nephritis, commonly on the surface but occasionally in the substance of the kidney, and due to compression of the renal tubules by fibrous tissue with subsequent dilatation. They are of no surgical interest.

2. **Polycystic Kidney.**—A condition in which the kidneys are much enlarged and converted into a series of cysts.

Gross Appearance.—The lesions are almost always bilateral, although usually more advanced on one side than the other. The kidney is en-

Fig. 263.—Polycystic kidney.

larged, it may be to three or four times the normal size, and, although preserving its general shape, is studded all over with cysts, so thin-walled that the yellowish or red color of the contents shines through, imparting a variegated hue to the tumor. On section the cysts, which vary greatly in size, are found to be scattered throughout the entire kidney (Fig. 263). Although occasionally opening into one another they never open into the renal pelvis. The contents vary; they may be thin or thick or viscid, yellow or amber, or dark brown from hemorrhage, and although usually non-urinous, they may occasionally contain uric acid and other organic constituents of the urine. In many cases it is so difficult to find any nor-

mal-looking kidney tissue that it seems incredible how a person could remain comparatively well with such an advanced bilateral condition. Localized suppuration is not uncommon.

Even *in utero* the cystic kidneys may attain a remarkable size. In one case which I examined the abdominal enlargement was so great that normal delivery was quite impossible, and the fetus had to be eviscerated. The abdominal cavity was almost completely filled by two enormous soft gelatinous masses representing the kidneys, weighing 780 grams; one of these was the size, shape, and appearance of a huge colloid goitre. The cysts were quite small. Other abnormalities of development were present in the shape of a meningocele and double clubfoot.

The *cause* is uncertain, but is most likely some error in development. The cystic condition may be merely a persistence of one stage of renal development (Kampmeier). The convoluted tubules which first develop
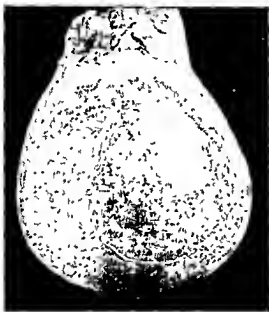
Fig. 264.—Solitary cyst of the kidney.

in connection with the collecting tubules are not permanent, but become detached from the collecting tubules and persist for a time as cystic structures. In the early embryo there are numerous cysts formed from the first generation of tubules. Normally these fetal cysts atrophy. If they persist they form a cystic kidney. Another theory is that the cysts are due to failure of the convoluted tubules to fuse with the collecting tubules.

Supporting the developmental theory is the fact that other developmental errors such as cleft palate and other similar malformations are by no means uncommon. Cystic formations in the liver occur with curious frequency, and the two conditions are undoubtedly due to a common cause. Occasionally small cysts are found in the pancreas.

Microscopically the cysts are lined by epithelium which in the large cysts is flattened, but cubical and even columnar in the smaller ones

15

The intervening kidney tissue usually shows a marked condition of chronic interstitial nephritis with extensive fibrosis.

The *clinical picture* is varied. There are two types, one of which is likely to come under the care of the surgeon, the other of the physician. In the first or surgical type the chief symptoms are pain, tumor and hematuria. The hematuria is due to hemorrhage occurring into a cyst and then communicating with the renal pelvis owing to destruction of the cyst wall. In the second or medical type the chief symptoms are renal insufficiency with arterial hypertension in over 50 per cent of the cases. The renal failure may come on quite suddenly. The disease has a strong tendency to be hereditary.

3. Solitary Cyst.—A solitary cyst of the kidney may remain small, in which case it will give rise to no symptoms. Occasionally, however, it may attain a great size (Fig. 264), in some cases being as large as a child's head. It is a disease of adult life, most of the cases occurring over the age of forty.

The cyst projects from the surface of the kidney, thus producing marked alteration in the shape of the organ. It is usually of a pale color. The contents are serous and contain albumin and salts but rarely traces of urea. Hemorrhage into the cyst may occur, and to such a condition the term hemorrhagic cyst has been applied. It is but natural that the larger cysts should often be mistaken for hydronephrosis.

The essential nature of the condition is unknown. It has been suggested by some that it is a congenital malformation, by others that it is a retention cyst due to interstitial nephritis. Needless to say convincing evidence to support either view is completely lacking.

DEVELOPMENTAL ANOMALIES

When we consider the extreme complexity of the kidney, the remarkable manner in which the pelvic portion derived from the Wolffian duct and the renal filter derived from the nephrogenic mass become fused together, and the very considerable migration upwards from the second sacral vertebra to the region of the second lumbar vertebra before the kidney finds its final abiding place, it is indeed not to be wondered at that abnormalities in development occasionally occur. The number of possible variations is legion, but those of chief surgical importance are the following: 1. incomplete development; 2. misplaced kidney; 3. fusion of the kidneys.

1. Incomplete Development.—There may be any grade of imperfect development, but we may consider three principal types: complete absence, congenital atrophy, and fetal lobulation.

Complete absence of one kidney is due in the great majority of cases to failure of development on the part of the bud from the Wolffian duct which gives rise to the pelvic portion. The ureter, therefore, is also absent. The condition, fortunately, is very rare, occurring onee in every 2500 cases. Its surgical importance is evident when the possible removal of the remaining kidney comes to be discussed. Death from anuria would result in the course of a few days. I once knew an asylum patient who was convinced that he had only one kidney, and at the autopsy I could find no trace of the right kidney. There was no scar of any kind.

Congenital atrophy may be of any degree. When at all marked it is accompanied by compensatory hypertrophy of the other kidney. The condition is again of surgical importance, because the small kidney, although otherwise normal, may be unable to carry on by itself should the other kidney be removed. The amount of urine produced is small, and therefore the total urea is diminished, although the percentage may be normal.

Fetal lobulation is a minor error of development, in which the kidney retains the lobulations characteristic of the fetal condition. The surface of the kidney is very irregular. The only importance of the condition lies in the fact that such a kidney shows with all other imperfectly developed kidneys a tendency towards tuberculosis, suppuration, and stone formation.

Fig. 265. – Horse shoe kidney.

2. **Misplaced Kidney.**—At any point of its upward progress the kidney may become arrested. As the vascularization of the kidney does not occur until its final resting place has been reached, it follows that when progress ceases too soon, the kidney becomes anchored by blood vessels in its abnormal position. The common positions, in their order of frequency, are at the bifurcation of the aorta, at the sacral promontory, and in the cavity of the pelvis. In the last-named position there are possibilities of trouble should pregnancy supervene. The condition should be suspected when a pelvic mass of uncertain origin interferes with the pregnant uterus.

A misplaced kidney must be carefully differentiated from a movable kidney. The latter has moved from a normal to an abnormal position. The former has never attained to a normal position.

3. **Fusion of the Kidneys.**—Once, it is said, in 1100 cases the nephrogenic masses on either side fuse together, and the Wolffian buds growing upwards form separate pelves and ureters for the mass. The condition

may be recognized at operation by noticing that the ureter passes down in front of the lower pole of the kidney.

Fusion mostly occurs at the lower poles, although in exceptional cases the upper poles may be united. The condition is called *horse-shoe kidney* (Fig. 265). The union may be merely fibrous, or a connecting band of renal tissue may pass across in front of the great vessels. Occasionally the fused kidneys may lie one above the other, giving rise to the "S" or *sigmoid kidney.*

Such a kidney is especially liable to be attacked by disease, and in a number of cases it has been possible to resect one half for tuberculosis or septic infection. It has indeed been said that a malignant growth may be confined to one side for a considerable time.

Leukoplakia of the Renal Pelvis.—Leukoplakia of the urinary tract is a rare condition, which may be confined to the pelvis of the kidney, may involve the mucosa of the pelvis, ureter, and bladder, or may be limited to the bladder. Both in the renal pelvis and in the bladder it is associated with and probably dependent upon chronic inflammation, and in both it may be a precursor of the non-papillary type of carcinoma, so that by some it is classed as a precancerous condition. The mucosa is wrinkled and skin-like. This epidermoid change is reflected in the microscopic picture, both a stratum corneum and a stratum granulosum being present. The process is usually regarded as a metaplasia from one type of epithelium to another, but Ribbert considers that it represents a development of embryonically misplaced cells. Some excellent illustrations of the condition will be found in a paper by Kretschmer.

THE URETERS

The ureter shares with the renal pelvis the pathological conditions to which the latter is liable. Suppuration, tuberculosis, stone, and neoplasms inevitably involve the duct of the kidney, and these conditions as they affect the ureter have already been discussed in their respective sections.

Congenital Dilatation of the Ureters.—This very remarkable condition is generally regarded as one of great rarity, and passes entirely unnoticed in the ordinary textbooks. It is probable, however, that it is commoner than is usually supposed, for I have encountered two examples in three years, in the second of which the correct clinical diagnosis was suggested, and Young and his associates at Baltimore record twelve cases admitted to the Johns Hopkins Hospital during a period of six years.

The condition occurs in male children, although very rarely a case has been described in adult life. The age in my first case was 2½ years, in the second case 12 years. The symptoms are those of gradually increasing urinary obstruction, with dilatation of the bladder and the ureters, an accumulation of residual urine, and failure of renal function. Our first case died of uremic coma; the second, which showed a blood pressure of 230, developed symptoms of pyelonephritis.

The autopsy findings were practically identical in both cases. On opening the abdomen a huge tube was observed running down each side. These at first glance were taken for the ascending and descending colon, but in reality they were merely the enormously dilated ureters (Fig. 266). In the first case the ureters were somewhat varicose and sacculated. The

kidneys showed a moderate degree of hydronephrosis, but were not greatly enlarged. The bladder was much distended and its wall showed extreme hypertrophy. A valvular obstruction was present in the posterior

Fig. 266.—Congenital dilatation of both ureters due to obstruction in the posterior urethra.

urethra. An instrument could be readily passed from below upwards, but not from above downwards.

It is now known that in most of these cases the essential pathology is a congenital obstruction of the posterior urethra, valvular in type, and so placed that the concave surface of the valve is directed upward, t

senting an obstruction to the outflow of urine. The exact nature of the obstruction membrane is still in doubt. In some cases it may be a persistence of the urogenital membrane of the embryo, in others an exaggeration of the normal folds of the posterior urethra associated with the verumontanum, in still others a persistence of fibrous strands which in the fetus may pass from the verumontanum to the roof of the urethra. In a few cases the cause had been a hypertrophy of the verumontanum.

Double Ureter.—The ureter is formed from a bud which grows up from the Wolffian duct. This may bifurcate in its upper half, giving a Y-shaped formation with one ureter below and two above. Or there may be two entirely separate ureters opening into two renal pelves. The former arrangement is the usual one. In rare cases there may be two separate kidneys on the same side.

Ureterocele.—This is a cystic swelling of the part of the ureter within the bladder wall due to prolapse of one or more of its coats. It forms a projection into the bladder associated with a pin-hole ureter which may be congenital or acquired. The cystoscopic picture is highly characteristic.

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THE LOWER URINARY TRACT

THE BLADDER

The bladder plays the part of a half way house between the upper and lower urinary tracts. It therefore runs a double risk of infection. As an offset to this it must be noted that the healthy bladder is peculiarly resistant to infections. Indeed it may safely be said that, with the exception of tumors, if a pathological condition be found in the bladder the strong probability is that it is not primary in that organ, and that the surgeon must seek elsewhere for the primary focus. This is true for cystitis, for tuberculosis, and for calculi, with the exception of those which occur in old men with prostatic retention. Finally, the bladder resembles the stomach in that it makes its voice heard above that of its neighbors, although usually it is they who are really suffering. Pus in the urine, painful micturition, and frequent micturition are apt to suggest bladder disease. They should not do so, but should rather be taken as an indication of renal disease.

The important diseases of the bladder are cystitis and tuberculosis, which may be regarded as secondary conditions, tumors which are primary, and calculi, which may be primary or secondary.

CYSTITIS

The immunity of the normal bladder to direct infection is quite remarkable. Pyogenic bacteria when introduced in large numbers rapidly disappear without producing any inflammation. There is, therefore, much truth in the remark that there is no such *disease* as cystitis. The real disease must be sought elsewhere, the cystitis being merely a complication which, on account of its obvious nature, forces itself upon the attention of the patient or the surgeon.

These remarks, however, only apply to the healthy bladder. A bladder already weakened by injury or disease is as liable to infection as any other organ. The most important of these predisposing causes are *injury and retention.*

Injury to the bladder may be done in the course of pelvic operations, especially hysterectomy. Fracture of the pelvis is frequently accompanied by cystitis. But perhaps the most important form of trauma is the presence in the bladder of foreign bodies such as a stone or tumor.

Retention may be due to stricture of the urethra, enlargement of the prostate, carcinoma, or paralysis of the bladder in tabes, injury to the spinal cord, and other nervous conditions. The retained urine undergoes decomposition and produces so much irritation of the bladder wall in addition to providing an ideal culture medium that infection is certain to occur if bacteria gain access.

Bacteriology.—The most common cause of infection is Bacillus coli, followed in frequency by staphylococci and streptococci. Two very troublesome organisms are B. proteus and B. pyocyaneus, because, being Gram-negative, they are resistant to penicillin. Fortunately they respond to treatment by streptomycin.

The general rule holds true that coccal infections are acute, bacillary chronic. In colon, typhoid, and gonococcal infections the urine is acid; in staphylococcal, streptococcal and proteus infections the urine is alkaline because these bacteria are ammoniogenic. A peculiar and important feature of the bacteriology of cystitis is that the flora of the bladder may change with a changed reaction of the urine. Thus a colon infection may replace a staphylococcus, or again a proteus may replace a colon infection. During treatment, therefore, both the reaction and the bacteriology of the urine should be carefully watched.

Mode of Infection.—Infection may reach the bladder from the urethra, from the kidney, or by extension from neighboring organs.

Infection from the *urethra* may be due to the passage of dirty instruments, or to the extension of a posterior urethritis.

Infection from the *kidney* is the cause of cystitis in at least 70 per cent of cases. In every case of cystitis, therefore, in which the cause is not quite obvious, the kidney should be suspected. When the renal source of infection is removed the cystitis will as a rule promptly clear up.

Infection from *neighboring organs* is of occasional occurrence. It may accompany pelvic inflammation in women, and also inflammation of the appendix and sigmoid.

Gross Appearance.—In *acute* cystitis, the mucous membrane is swollen and intensely red and congested. The normal glistening appearance is lost, hemorrhages are dotted here and there, small ulcers may develop, flakes of muco-pus and shreds of epithelium adhere to the surface, and in the trigone there may be the appearance of tiny clear cysts to which the name of bullous edema has been given. The mucous membrane is freely movable on the underlying muscle.

In chronic cystitis the appearance varies much as it does in chronic cholecystitis. The bladder may show concentric thickening of its wall with corresponding reduction in the size of the cavity. This occurs when the inflammation is marked and there is no retention. The thickening is an inflammatory interstitial one, and is not due to any extent to a hypertrophy of the muscular tissue. If, on the other hand, retention be marked and inflammation only slight, dilatation of the cavity with atrophy of the wall will occur.

The mucous membrane varies in appearance in different parts of the bladder. It has lost its smooth, uniformly pink appearance, and is rough, dull in hue, and mottled with the brown remains of old hemorrhages. In places it may be ulcerated, but elsewhere hypertrophied so as to form granulomatous masses which project into the lumen. Irregular ridges spoken of as trabeculae run hither and thither across the bladder, and between these the wall may become pouched into diverticula. The mucous membrane is firmly attached to the muscle, owing to fibrous changes in the submucosa.

Microscopic Appearance.—In the acute stage the changes are for the

most part confined to the submucosa, which is much congested and infiltrated with the cells of acute inflammation. The superficial layers of the epithelium may be desquamated, but the deeper layers remain intact, except when ulceration of the mucosa has developed over submucous hemorrhages. The muscle is unaltered.

In the chronic stage all the coats are involved. The characteristic feature is a diffuse fibrosis, most marked in the submucosa. The mucosa is ulcerated in places, but in others it is the seat of an abundant formation of exuberant granulation tissue covered by epithelium, and giving rise to the polypoid excrescences already mentioned. The submucosa is densely fibrosed, and the fibers of the muscular coat are separated by an enormous amount of connective tissue.

Leukoplakia.—In some cases of chronic cystitis the transitional epithelium of the bladder undergoes a metaplasia into cornified epithelium, a condition known as leukoplakia. The change is essentially patchy, and the pale, clean-cut areas are sharply defined from the surrounding mucosa. These lesions, as in the tongue, may form the starting point of an epithelioma.

Cystitis Cystica.—Cysts may develop in the mucosa of the bladder, ureter or renal pelvis, a condition known respectively as cystitis cystica, ureteritis cystica, and pyelitis cystica. As a result of long-standing chronic irritation there occurs a downward projection, from the inferior layer of the epithelial cells of the mucosa, of epithelial nests known as Brunn's nests. A lumen develops in the center of these nests as a result of a secretory process, and multiple small cysts are formed lined by flattened epithelium; these cysts project on the surface of the mucosa. The mechanism is similar to that responsible for the formation of subserous peritoneal cysts on the Fallopian tubes, appendix, etc. In some cases the lining cells may assume a glandular character, becoming more columnar with basally placed nuclei; these cells secrete mucin. The resulting condition is known as cystitis, ureteritis, or pyelitis glandularis. It has been suggested that the new gland formations may act as the starting point of adenocarcinoma of the bladder. It seems much more probable that these glandular lesions are the result of metaplasia than that they are derived from epithelial cells of the large intestine which have been misplaced during embryological development.

Cystitis Emphysematosa.—This is a rare form of cystitis accompanied by the evolution of gas. Small, transparent, gas-filled cysts are present in the mucosa and submucosa. They seem to originate in the lymph vessels. Bacteria, possibly B. coli, are believed to be responsible.

Hunner's Ulcer.—This condition goes under a variety of names, such as interstitial cystitis, panmural ulcerative cystitis, localized submucous fibrosis, etc., indicating clearly the obscure nature of the lesion. The affected area shows marked inflammatory thickening, and in the center there is a minute, exquisitely tender ulcer, often little more than a superficial erosion. The ulcer, together with the symptoms, may come and go, so that it is known as the "elusive" ulcer. Microscopically there is edema, congestion, and round-cell infiltration, most marked in the submucosa, but sometimes involving all the coats. The cause and nature of the condition are unknown. It does not appear to be a straight infection; the urine is usually free from pus or bacteria. It may be allergic or neurogenic in character. The disease, which is very much commoner in women, is of long duration and marked by periodic attacks of severe or excruciating pain on distension of the bladder, frequency of micturition, and great decrease of bladder capacity. In extreme cases urination occurs every few minutes, and the patient may become a nervous wreck.

TUBERCULOSIS OF THE BLADDER

For practical purposes it may be said that tuberculosis of the bladder is never primary. It is always secondary, to tuberculosis of the kidney in the great majority of cases, to tuberculosis of the prostate, seminal vesicles, and epididymis in a few cases, and very rarely to tuberculosis of adjacent organs such as the Fallopian tubes.

In renal cases the disease commences at the ureteric opening, in prostatic cases it begins at the neck of the bladder. Only too often, however, by the time the patient presents himself for treatment the disease has spread to such an extent that the *entire* trigone is involved. The initial lesion is a tiny, white, translucent tubercle covered by epithelium and situated in the subepithelial connective tissue. Soon, however, ulceration of the overlying epithelium occurs. The *tuberculous ulcer* is characteristically round, with ragged, overhanging edges, and a grey, shaggy floor. Although occasionally covering a considerable area it is seldom deep, and perforation is almost unknown.

The infection is at first a pure tuberculous one, but sooner or later a mixed infection is sure to occur, and the condition becomes one of tuberculous cystitis. Removal of the offending kidney will be followed, in the earlier cases, by recovery of the bladder lesions in the course of a few months. In the later and more advanced cases the duration may be for years or it may be forever.

STONE

The factors concerned in the formation of urinary calculi, together with the different varieties and composition of such calculi, have already been discussed in connection with stone in the kidney. In this section, therefore, only the features peculiar to vesical calculus will be considered.

Stone in the bladder may be primary or secondary. It may commence in the bladder, or, first forming in the kidney, it may pass down the ureter and become a vesical calculus. A primary stone is likely to consist of phosphates or urates. The phosphatic calculus, which is the common variety, is associated with those conditions such as stricture and enlarged prostate which give rise to retention and an alkaline urine. An oxalate stone in the bladder has probably had a renal origin.

The stone may be single or multiple. In the former case it is round or or oval. In the latter the stones are cuboidal and frequently faceted.

Spontaneous fracture is a rare and interesting occurrence, one, moreover, which has on occasion been turned to good account by vendors of wonder-working lithia waters. The exact cause of the fracture is not known, but it is probably dependent on an alteration in the internal tension of the stone resulting from a marked change in the specific gravity of the urine.

Reference has already been made to the effect of the presence of a stone upon the bladder. A stone in the bladder is a powerful predisposing cause to cystitis as long as the stone is present. The pressure of the stone may produce a serious degree of ulceration of the bladder wall.

EPITHELIAL TUMORS OF THE BLADDER

Epithelial tumors of the bladder may be innocent or malignant. They may be divided into three main groups: (1) papilloma (benign), (2) papillary carcinoma, (3) nonpapillary carcinoma. Papillary carcinoma is the most common and nonpapillary carcinoma the least. The line of distinction between the first and second groups is sometimes very thin, and even with careful study of a specimen removed for biopsy it may be

extremely difficult to decide the question of malignancy. The benign papillomas have a tendency to become implanted in other parts of the bladder and in the suprapubic wound. When a benign papilloma is destroyed another papilloma may develop in the bladder. The removal of a papilloma may be followed by the appearance of a carcinoma, or a benign papilloma may become malignant. Such facts should make both the clinician and the pathologist cautious about expressing unduly dogmatic opinions regarding the epithelial tumors of the bladder. The wise attitude to adopt is that which is well expressed by Aschner when he says that the verdict should be "guilty until proved innocent."

The *etiology* of bladder tumors would not be worth discussing until we know something of the etiology of tumors in general, were it not that these growths provide three interesting examples of the relation of chronic irritation to neoplasia. First, it is well known that workers with aniline dyes are peculiarly susceptible to bladder tumors, owing, it has been supposed, to the irritating effect of the dye excreted in the urine. Second, the leukoplakia occasionally resulting from chronic cystitis may become the site of an epidermoid carcinoma. On the other hand no relationship has ever been shown to exist between carcinoma and stone in the bladder. The third example is Bilharzia carcinoma. The presence in the bladder wall of the sharp-spined ova of Bilharzia hematobium is often associated with carcinoma. For this reason cancer of the bladder is particularly common in Egypt, a country whose people are infested with Bilharzia.

With regard to aniline dye cancers of the bladder, it is of interest to note that before 1914 most of the cases in aniline dye workers occurred in Germany, but since the war there have been as many as 23 fatal cases in one year in one English factory and 25 in a large American plant. The lung is the chief route of infection, but in addition to being inhaled the agent may be ingested or may enter through the skin. The tumors are often multiple and vary in malignancy from benign villous papillomas to infiltrating carcinomas. The carcinogenic agent in the dye is now known to be beta-naphthylamine. Dogs fed or injected with this substance develop tumors of the bladder but not of the kidney (Hueper et al.). It is of interest to note that the injection of beta-anthraquinoline produces kidney tumors but not bladder tumors (Sempronj and Morelli).

1. Papilloma.—A benign papilloma of the bladder is a soft, shaggy, villous tumor consisting of a number of finger-like processes covered by many layers of epithelial cells. The villi, which usually spring directly from a small circumscribed area of the mucosa, are more fragile and delicate than the fronds of any fern, and when seen with the cystoscope swaying to and fro with every swirl of the fluid in which they float they have the grace and beauty of a sea-anemone. In other cases the villi arise from a well-defined pedicle, but they themselves are then much more short and squat, so that the growth has a raspberry appearance. The mucosa from which the tumor springs is not attached to the muscular coat.

The connective tissue stroma of the villi is exceedingly delicate and vascular, consisting largely of capillary loops. The epithelial cells are arranged in palisade fashion at right angles to the stroma, being well demarcated from it by a basement membrane. The cells are several

layers deep, and are very regular in size, shape, and the depth of staining of the nuclei (Fig. 267).

The usual *sites* are (1) just external to the ureteric openings, (2) at the neck of the bladder, and (3) more rarely in the vault. It is not uncommon to find *multiple growths*, owing to the tendency of the tumor to become implanted on the bladder mucosa. Such a growth does not need to be malignant, any more than multiple polypi of the stomach need be malignant. At the same time the tumor should be regarded as "guilty till proved innocent." The age incidence is between 30 and 50, and the disease is much commoner in men than women.

The chief *symptom* is painless hematuria. This is easy to understand when the extremely vascular and fragile nature of the villi is considered, and how readily they may be broken by contractions of the bladder.

Fig. 267.—Papilloma of bladder. × 80.

Fig. 268.—Papillary carcinoma of bladder.

2. **Papillary Carcinoma.**—This is the commonest of the epithelial tumors of the bladder (Fig. 268). It usually originates from a benign papilloma, the change occurring in any part of the tumor and not necessarily at the base as used to be thought. It may be divided into non-infiltrating and infiltrating forms. (a) The *noninfiltrating papillary carcinoma* offers the hardest problem for the pathologist. It is indistinguishable cystoscopically from the benign papilloma, from which, indeed, most of the cases seem to develop. The cytological changes may be so marked that a diagnosis of malignancy is easy, or so slight that it is extremely difficult. The points to be looked for are irregularity in the size and appearance of the cells, large cells with deeply stained nuclei, pyknosis of the nuclei, numerous mitotic figures (a few may be seen in the benign papilloma), and loss of the palisade arrangement. The basement membrane may be intact, and yet tumor cells may be found in the vessels of the stroma, so

that these vessels should be carefully examined. As the tumor increases in size necrosis and infection are likely to supervene, and the bladder may finally be filled with a large, fungating, breaking-down mass. (b) In the *infiltrating papillary carcinoma* there is invasion of the stalk of the tumor and of the bladder wall. In these cases there is a tendency to squamous metaplasia on the part of the tumor cells.

3. **Nonpapillary Carcinoma.**—This is the least common variety. The tumor spreads deeply through the bladder wall and widely under the mucous membrane. Necrosis and marked ulceration are prominent features. There may be no projecting mass on the surface, but a carcinomatous ulcer with raised thickened edges. The tumor may be medullary or scirrhous in type. Occasionally an epidermoid carcinoma develops on top of a leukoplakia. Still more rarely the tumor is an adenocarcinoma which has developed from the so-called glands of von Brunn in the trigone of the bladder.

Spread.—The papillary form of carcinoma remains localized for a considerable time, but is apt to set up implantation growths in other parts of the bladder. In the infiltrating varieties, both papillary and nonpapillary, there is spread to the internal iliac and lumbar lymph nodes. Blood spread is less common, but may cause metastases in the lungs and liver, and occasionally in the bones, especially the vertebrae. Death is likely to occur from obstruction of the ureters and septic infection of the kidneys before there is time for extensive metastases by the blood stream.

The *biopsy* is of great value in bladder tumors, but often presents the pathologist with a knotty problem. When the specimen is removed by the cystoscope, as is usually the case, fulguration should not be used, as the resulting distortion of tissue is so great that the histological picture may be greatly altered, and the significant but slight cellular changes which may be present in the papillary growth may be completely missed. These changes have already been enumerated. The old idea that the malignant change always first showed itself as an epithelial invasion of the pedicle is now known to be incorrect. The fatal metamorphosis may begin in one of the villi, leaving the base untouched. It is desirable to examine sections from various parts of the tumor in difficult cases.

The *prognosis* depends a good deal on the grade of the carcinoma, as in other parts of the body. In the grade 4 cases early and widespread metastases may be expected, whilst the grade 1 cases remain localized for a long time. The radiosensitivity varies directly with the grade; the higher the grade, the greater the sensitivity of the tumor. It is a mistake, however, to think that prognosis can be determined solely by grading, for the presence or absence of infiltration is as important as the cytological differentiation.

Sarcoma is a very rare condition. It is always sessile. It may be round-celled or spindle-celled.

Myxoma is confined to children. The tumors may be multiple, and are usually pedunculated.

Dermoid cyst may occur in the wall of the bladder, giving rise to that pathological curiosity, *pilimiction*, or the passage of hair in the urine.

Diverticulum of the Bladder.—This is a pouch-like opening which communicates with the bladder by a narrow mouth. It may be congenital or acquired. The congenital form is quite rare, and occurs in infants and young children. The acquired variety is met

with in men usually over the age of fifty; it is very uncommon in women. It is usually associated with some form of urethral obstruction, such as stricture or enlarged prostate. There must be some other factor, perhaps congenital weakness of the bladder wall in one area. The usual type is therefore a pulsion diverticulum. In rare cases there may be a traction diverticulum, owing to adhesions to neighboring organs or involvement of the bladder in a hernia.

The usual site is on the lateral wall of the bladder near the opening of the ureter. Sometimes the diverticula are multiple. The pouch may be quite small, or it may be larger than the bladder itself (Fig. 269). The opening is small and sharply defined. At first the wall is formed by all the coats of the bladder, but as the sac enlarges the muscle becomes thinned out over the fundus, and may eventually disappear.

The *effects* are varied. Owing to the disappearance of the muscle in the wall of the sac, the diverticulum is unable to empty itself, the urine becomes stagnant, and infection (cystitis) is extremely likely to occur. These conditions are ideal for the formation of a phosphatic calculus. The opening of the ureter may be dragged upon or pressed upon, so

Fig. 269.—Two large diverticula of the bladder.

that hydronephrosis results or an ascending infection of the kidney. Carcinoma may occasionally develop in the diverticulum.

Patent Urachus.—The urachus is a solid cord passing from the apex of the bladder to the umbilicus and representing a portion of the allantois. This may remain patent throughout its entire course, in which case urine will issue from the umbilicus. Or only a portion may remain patent, the remainder becoming obliterated. The latter variety may open internally, it may open externally, or both ends may be closed while the intermediate part remains patent.

Ectopia Vesicae.—Ectopia of the bladder is happily a rare condition, for the lot of the unfortunate sufferer is one of great misery. Owing to a defect of development the anterior wall of the bladder is deficient, the anterior abdominal wall is split with separation of the recti, and the interior of the bladder is exposed. The urine can be seen trickling from the openings of the ureters.

As a therapeutic measure the ureters may be transplanted into the sigmoid, but infection of the kidneys is very liable to occur. As already pointed out, this infection does not pass up in the lumen of the ureter.

PATHOLOGICAL BASIS OF SYMPTOMS OF RENAL DISEASE

At this stage it may be allowable briefly to consider the leading symptoms of a patient suffering from a surgical disease of the kidney, and to

determine to which pathological lesion they are most likely to be due. These symptoms are frequent and painful micturition, blood in the urine, and pus in the urine.

Frequent and Painful Micturition.—Either the frequency or the pain may be absent, but usually they are combined. This symptom may point to disease in the urethra, the bladder, or the kidney; in the urethra to a posterior urethritis, gonorrheal in nature; in the bladder to cystitis, tuberculosis or stone; in the kidney to pyelonephritis, tuberculosis, or stone. The bladder is the organ against which suspicion is usually directed. Frequent and painful micturition is, however, rather a renal than a vesical symptom.

Blood in the Urine.—The blood may come from the urethra, the bladder, or the kidney. In the first case the blood comes at the *beginning* or urination and is of a bright red color, in the second it comes in greatest abundance at the end of urination and may contain clots, in the third it is *intimately mixed* with the urine, to which it imparts a smoky color.

Urethral hematuria is due to injury or acute inflammation of the urethra or prostate.

Vesical hematuria may be due to a stone in the bladder or to a tumor. In the latter case the hemorrhage is due to the delicate and highly vascular processes being injured by the contraction of the bladder. A tuberculous ulcer in the bladder may give rise to hemorrhage. Rare causes of vesical hematuria are varicose veins and Bilharzia hematobium.

Renal hematuria may be due to acute Bright's disease, chronic congestion of the kidney, paroxysmal hemoglobinuria, and other medical conditions. Surgical causes are rupture of the kidney, stone, and tuberculosis. In addition any inflammatory condition such as pyelitis or pyelonephritis may give rise to bleeding, but the associated pyuria is usually so great as to overshadow and obscure the hematuria.

Of special interest is the condition known as *essential hematuria,* a term intended to indicate that the bleeding is, as it were, idiopathic and can be traced to no known lesion. The blood is abundant, and readily recognized by the naked eye; indeed the urine may be dark red in color. The bleeding is intermittent, and in the intervals, which may last for weeks or months, no blood can be found. One peculiar feature is that it is strictly unilateral.

Although a cursory examination may reveal no cause for the hematuria, the work of Israel, published many years ago, showed that most if not all cases have a definite organic basis. In many cases this is a unilateral nephritis, which may be either focal or diffuse. The latter is usually of the interstitial variety. A varicose condition in one of the renal papillae is sometimes found, due probably to obstruction from interstitial nephritis. Hunner has drawn attention to the importance of stricture of the ureter as a cause of essential hematuria. The stricture itself is due to inflammation secondary to some distant focus of infection. The aching or colicky pains which are not infrequently present may be explained by the presence of a ureteral stricture.

Finally one may have to look outside the urinary tract for the cause of the hematuria, either to systemic conditions such as the blood diseases, or to lesions of structures immediately adjacent to the urinary tract such

as the appendix. In the latter case the hematuria is usually the result of a focal glomerulonephritis affecting one or both kidneys due to a true blood infection. The principal *causes* of hematuria are shown in Fig. 270.

Pus in the Urine.—Any inflammatory condition in the urethra, the bladder, or the kidney may give rise to pyuria.

If the pus comes chiefly at the *beginning* of micturition and the urine is acid, the most probable causes are gonorrheal urethritis and prostatic abscess.
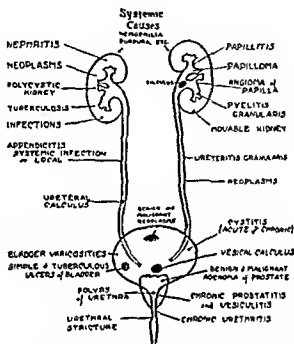
Fig. 270.—*Various sources of hematuria.* (Eisendrath.)

If the pus comes chiefly at the *end* of micturition and the urine is alkaline, the cause is cystitis. The urine may, however, be acid in a pure infection with either Bacillus coli or the tubercle bacillus.

If the pus is *intimately mixed* with the fresh urine and the reaction is acid the pus comes from the kidney, and is due to pyelitis or pyelonephritis, tuberculosis, or stone. The reaction must be tested while the urine is still fresh, else ammoniacal decomposition may set in and the reaction may become alkaline.

THE PROSTATE

The prostate gland, although forming an integral part of the lower urinary tract, is a purely sexual organ, and plays no part in the act of urination. Owing to its anatomical situation, however, pathological conditions which in themselves might be regarded as trivial may produce disastrous effects on the entire urinary system.

The important diseases of the prostate are acute and chronic inflammation, enlargement of the prostate, tuberculosis, and cancer.

PROSTATITIS

Inflammation of the prostate may be acute or chronic.

Acute Prostatitis.—This, in the great majority of cases, is due to infection with the gonococcus. An acute gonorrheal urethritis involving the posterior urethra inevitably spreads to the prostate. Three degrees of inflammation may be set up.

Catarrhal inflammation is the most common condition. The ducts are filled with desquamated epithelium and with varying numbers of leucocytes.

Purulent follicular inflammation is a more severe grade of inflammation in which the ducts become blocked with purulent exudate, behind which small abscesses form and discharge into the urethra.

Purulent diffuse inflammation occurs when general invasion of the gland by the gonococcus results in widespread suppuration with destruction of glandular tissue and the formation of abscesses which may occupy the greater part of the prostate. Such an abscess may burst into the urethra, into the rectum, or upon the surface of the perineum. A diffuse cellulitis of the surrounding tissues is a common complication.

Chronic Prostatitis.—This may be a sequel to an acute inflammation which has gradually subsided. More frequently, however, it is gradual and insidious in onset, although due, as in the case of the acute form, to infection with the gonococcus. The gland presents the changes which would be expected from general principles. The ducts and acini are dilated and filled with catarrhal cells. Areas of round-cell infiltration are scattered here and there. Fibrosis and scar formation are present in varying degree in different parts of the gland. The prostate is unduly hard and of varying size, in some cases smaller, in others larger than normal.

It is only to be expected that in such chronic cases the gonococcus will be associated with or replaced by other bacteria. Staphylococci, streptococci, and Bacillus coli are the most frequent secondary invaders.

It is commonly believed that the prostate is one site of so-called focal infection as a result of which secondary lesions (chronic arthritis, etc.) may be produced in distant parts of the body. In 581 cases of chronic prostatitis Moore found no evidence that this condition is associated with chronic diseases which are attributed by some to focal infection

ENLARGEMENT OF THE PROSTATE

Enlargement of the prostate is a convenient non-committal term, although many others such as hypertrophy, adenoma, and adenomyoma are in common use. Perhaps the best name is nodular hyperplasia, as suggested by Moore in his excellent review of the subject. There can be little doubt that the condition is due to stimulation resulting from the imbalance of the testicular hormones which develops with advancing years.

Prostatic enlargement is one of the best examples of a disease process with a very well defined age incidence. Only under the rarest circumstances does it occur in early life. It is essentially a disease of the years from 50 to 65.

Some degree of enlargement of the prostate after the age of 50 is the rule rather than the exception. As Sir Benjamin Brodie put it long ago:

"When the hair becomes grey and thin, when there is formed a white zone about the cornea, at the same time ordinarily, I dare say invariably, the prostate increases in volume."

Fortunately enlargement of the prostate is by no means synonymous with the development of symptoms. There is no direct relation between the degree of enlargement and the severity of the symptoms. A prostate weighing as much as 40 grams and yet producing no symptoms may be found accidentally at autopsy.

Walker points out the interesting fact that prostatic enlargement is common amongst domestic animals with the onset of old age. This is particularly well seen in the case of the dog. The condition has a wide distribution throughout the animal kingdom.

The passage of the ejaculatory ducts downwards and forwards through the gland divides it into two portions, a posterior lobe and an anterior part made up of the anterior, middle and lateral lobes. The posterior lobe deserves to be thus separately distinguished, for it takes no part in hypertrophy of the prostate, although it may become the seat of carcinoma.

Morbid Anatomy.—The changes are of two main types: (1) an overgrowth of the glandular elements, and (2) a diffuse production of fibrous tissue. Depending upon which of these happens to predominate the prostate will be large and soft, or small and hard. One part of the gland may show one condition, another the other.

In most cases the enlargement is due to the formation of one or more nodules, somewhat spongy in appearance, and well delimited from the remainder of the gland. These nodules usually fuse together to form one mass which can readily be shelled out. This mass enlarges at the expense of the rest of the organ, which it compresses to such an extent that it forms for itself a false capsule consisting of fibrous tissue with a little of the old muscular tissue still left. A line of cleavage can readily be set up between the mass and this false capsule. In those cases in which a diffuse fibrosis rather than a glandular hyperplasia dominates the picture such separation is usually impossible.

The enlargement may involve any part of the gland except the posterior lobe. Two lateral lobes and a middle lobe are frequently formed, or the overgrowth may be confined to the middle lobe. Randall, whose monograph on the subject should be consulted, divides the lesions into a number of groups, of which the three most frequent are hypertrophy of both lateral lobes, hypertrophy of the posterior commissure, and hypertrophy of the subcervical lobe. The last two constitute the so-called "middle lobe enlargement." *Bilateral lobe hypertrophy* first compresses the urethra until it becomes a mere slit and may later herniate through the internal sphincter and protrude into the bladder as an intravesical growth, although this does not necessarily occur (Fig. 271). In *posterior commissure hypertrophy* there is overgrowth of the glandular tissue which lies below the floor of the urethra and joins together the lateral lobes; this is the anatomical middle lobe. The immediate result is elevation of the posterior vesical lip, but the deeply buried glandular mass is often missed. *Subcervical hypertrophy*, the commonest type, is overgrowth of a small group of gland acini which lies between the posterior

vesical lip and the verumontanum. This group is just submucous and entirely outside the true prostatic capsule. The mass projects first into the lumen of the urethra and then through the internal sphincter, and as its attachment is composed only of its own ducts and its only covering is the mucous membrane, pedunculation appears early and remains a characteristic feature. Randall in comparing the posterior commissural and subcervical forms remarks that "commissural hypertrophy assumes a heavy, broad-based, stolid, cumberous, bulky, massive obstruction, and subcervical hypertrophy, characteristically pedunculated, appears as a dainty, artistic, symmetrical, poised and graceful lobe."

The *fibrous median bar* must not be confused with prostatic hypertrophy. It is an obstruction to the vesical outlet from a thin and abrupt

Fig. 271.—Bilateral lobe hypertrophy of prostate.

elevation of the posterior vesical lip with sclerosis of the internal sphincter. It appears to represent the end results of an inflammatory fibrosis from an underlying chronic prostatitis. The clinical result is urinary obstruction without prostatic hypertrophy.

The *microscopic appearance* is one of glandular hyperplasia combined with fibrous and muscular overgrowth. The first lesion is hyperplasia of the stroma around the ducts, acini and urethra. The nodules are derived from the stroma and glands of the so-called inner group of glands, *i. e.*, the periurethral glands and acini anterior and medial to the ducts of the lateral lobes. True middle lobe involvement is less common. The stroma is richer in smooth muscle than normal, but has less elastic tissue. The epithelial cells show less evidence of secretory activity. There may be a development of masses of lymphoid tissue, often mistaken for evidence

of inflammation. There appears to be a great proliferation and budding of ducts and acini (Fig. 272), and the picture at once recalls the somewhat similar appearance seen in thyroid hyperplasia and in chronic mastitis. The epithelium is cylindrical in form, and papillary projections may be so abundant as nearly to fill the glandular spaces. In other cases the chief increase is in fibrous and muscle tissue; here the prostate is likely to be very firm and not much enlarged. Corpora amylacea may be present, but not in greater abundance than in the normal prostate.

The nature of the condition has long been a subject for debate. Many attempts have been made to prove a relationship to gonorrhea, but the evidence is altogether too inconclusive to tarnish the character of respectable old gentlemen. Reference has already been made to the similarity of the microscopic picture of this condition to that of chronic mastitis. It

Fig. 272.—Hyperplasia of prostate. × 120.

is now certain that both are due to hormonal stimuli. The injection of estrin causes hypertrophy of the prostate in animals identical with that which occurs in man. In mice the animals develop urinary obstruction with distension of the bladder and ureters and hydronephrosis. The prostate of the human male child is enlarged at birth, probably due to the maternal estrin which is present in the urine for the first few days of life; soon this enlargement disappears. The injection of male (testicular) hormone has the opposite effect to that of estrin. The germinal epithelium seems to exert an inhibiting effect on prostatic growth, so that the gland develops up to puberty and after the age of 50, but not in between. It is probable that the germinal epithelium and the interstitial cells of the testis act in opposite ways. Destruction of the germinal epithelium by means of X-rays leads to hypertrophy of the prostate as the inhibiting

action of that epithelium is lost. On the other hand castration, which removes both types of cells, leads to atrophy of the prostate. It is becoming evident that in the near future the control of prostatic hypertrophy will be by means of hormones.

Effects.—Although enlargement of the prostate in itself is a perfectly innocent condition, it may readily be responsible for the death of the patient owing to the secondary changes which it sets up. Every prostatic is threatened by retention followed by infection. Although the bladder symptoms make his life one of extreme misery, yet it is the effect on the kidney which is ultimately responsible for his death.

The *prostatic urethra* may be much distorted. In addition to being elongated it may be compressed or rendered tortuous. This in itself may produce a certain amount of obstruction.
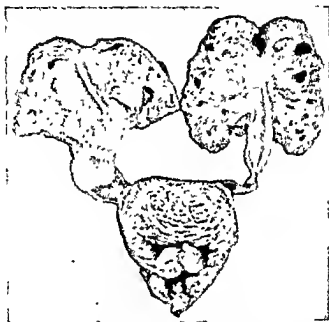
Fig. 273.—Effects of enlargement of the prostate.

The *bladder* cannot be completely emptied. In some cases this is due to the ball-valve action of the middle lobe. A more important and constant factor is the elevation of the urethral orifice above the level of the bladder floor owing to the upward growth of the prostate. The effect is the same as if the outlet of a tank were moved from the bottom to a point some distance up the side. Finally, the vesical sphincter may be so dilated by the enlarging mass that it becomes quite incompetent. The effect of all this is to produce a retention overflow. The tank is never empty, and when the urine reaches the level of the outlet it pours over.

As a result of the obstruction the bladder at first becomes hypertrophied, but later dilated. The muscle bands become transformed into thick trabeculae which give the wall a ribbed appearance. As dilatation proceeds the wall between these trabeculae becomes pouched into a series

of false diverticula. Later the dilatation extends to the ureters and kidneys, producing double hydronephrosis (Fig. 273) with a corresponding degree of renal insufficiency, as manifested by a lowered phthalein output and by increase in the non-protein nitrogen of the blood. When this inadequacy has reached an advanced stage any sudden removal of the constant high pressure, such as may follow the operation of prostatectomy, is liable to be accompanied by grave symptoms of suppression and uremia. In these cases a blood urea of over 100 mgms. per 100 c.c. must be taken as a contraindication to operation.

Even though the damage to the kidneys is only slight, the back-pressure is often associated with arterial hypertension. Complete drainage of the bladder in urinary retention brings about a marked fall in the systolic blood pressure in the first 48 hours. During this period the functional efficiency of the kidney is diminished, as shown by a rise in the blood urea. The fall in the systolic pressure may be as great as 80 mm. O'Conor has shown that if drainage is good, the blood pressure becomes fixed at a definite level, the renal function improves, and conditions for operation are much more favorable.

Infection is certain to occur sooner or later should the patient have to adopt a catheter life, for the pool of stagnant residual urine is an ideal culture medium awaiting the arrival of even one microorganism from without. The effect of infection is threefold: (1) the production of cystitis, (2) the probable formation of a vesical phosphatic calculus, and (3) the development of a pyelonephritis or pyonephrosis with a degree of renal insufficiency which eventually results in the death of the patient.

TUBERCULOSIS OF THE PROSTATE

Owing to its anatomical situation the prostate may be infected with tuberculosis either from the urinary or from the genital tract. In an extensive investigation, however, Moore concludes that tubercle bacilli usually reach the prostate by way of the blood stream. The prostatic lesion is secondary to other urogenital tuberculosis in less than 20 per cent of cases. The subject will be considered in greater detail when genital tuberculosis comes up for discussion. The disease process may commence in the prostate instead of spreading from the kidney or the epididymis.

Experimental work has shown that the initial lesion is found just under the epithelium lining one of the ducts. Miliary tubercles are formed which increase in size, giving rise to caseous masses scattered throughout the gland. Although the early lesions are probably on the same side as the infected epididymis, by the time the disease is diagnosed clinically the greater part of the gland is involved, and firm nodular masses can be felt on both sides. Occasionally there is a diffuse tuberculous infiltration without nodule-formation. If caseation is extensive a tuberculous abscess is formed, which may burst either into the urethra or upon the surface. In the latter case a tuberculous fistula will result.

By the time that tuberculosis of the prostate can be diagnosed clinically both seminal vesicles will always be found to be involved.

Tuberculosis of the prostate resembles *enlargement of the prostate* in that it gives rise to no distinctive symptoms *per se*. The symptoms of the

patient are those of tuberculous cystitis, or he may come complaining of an enlarged testicle.

Once tuberculosis has become established in the genito-urinary tract it seldom undergoes spontaneous cure, but when the kidney or the epididymis which is the source of the infection has been removed the disease in the prostate may become quiescent or may actually clear up completely.

CANCER OF THE PROSTATE

The prostate is one of the common sites of cancer in men above the age of forty-five. This fact is evident not only from clinical observation but also from autopsy investigation. Thus Rich found latent (unsuspected) carcinoma in 14 per cent of routine autopsies over the age of 50, and Moore reports the following figures: from 61 to 70 years, 23 per cent; from 71 to 80 years, 21 per cent; from 81 to 90 years, 29 per cent. In 388 prostates removed for benign hypertrophy McGavin found 20 carcinomas. It should be pointed out that these figures are the result of minute examination of each prostate, because the malignant focus may be very small. In a series of 50 unselected consecutive autopsies on men over 50 years of age Baron and Angrist found occult carcinoma in 46 per cent. These occult tumors are small, slow growing, and probably exist for many years without causing symptoms and without metastases.

The idea that cancer occurred as a malignant degeneration of an already hyperplastic gland has had to be abandoned, although hyperplasia may be present as an associated condition in about 50 per cent of the cases. Moreover carcinoma commences in that portion of the gland which is free from the ordinary form of hyperplasia, namely the posterior lobe, although from there it may invade adenomatous masses in the lateral and middle lobes. The usual age incidence is about a decade beyond that of the benign form.

The following description of the pathology by Young is so concise and at the same time so complete that it is given *in extenso*.

"We feel convinced that carcinoma of the prostate does not result as a degeneration of a previously benign adenomatous process; that in about half of the cases it develops where no hypertrophy is present; that in such cases the prostate is little if at all enlarged; that the carcinomatous growth follows planes of least resistance; that it is very slow in invading fibrous capsules both of the prostate itself and also of hypertrophied lobes; that the mucosa and submucosa of both urethra and bladder are also very resistant to it; that the most common site for the beginning of cancer is in the posterior subcapsular stratum or lobe, and that from there it may invade the rest of the prostatic glandular tissue, or it may travel upward, escaping from the upper end of the prostate in the region about the ejaculatory ducts, and between the fascia of Denonvilliers posteriorly and the trigone anteriorly; that in its further growth the seminal vesicles and vasa deferentia may not become infiltrated, but in some cases their lumina may become filled with cancer cells and, in the case of the vasa deferentia, these may extend upward for a long distance, the outward walls of the vas remaining apparently intact; that the muscle of the trigone and bladder and also the peritoneum may be invaded from this subtrigonal involvement; and, finally, that the fascia of

Denonvilliers, which gives the prostate its most dense capsule posteriorly, is a most effective agent in preventing involvement of the rectum and periprostatic structures." (Modern Urology—Cabot, Vol. ii, p. 659.)

The chief choracteristic of the growth is its consistency, which is as hard and dense as thot of a scirrhous tumor of the breast. When cut into it imparts the same gritty sensation to the knife as is felt in breost cancer. The surface is dense, dry, without lobulation, and small yellowish islands composed of carcinomatous cells are seen separated by the more translucent fibrous tissue.

The *microscopic picture* is a varying one, but two main types of growth are encountered, the scirrhous and the adenocarcinomatous. The former is much the more frequent. The scirrhous form is similar to that seen in the breast and elsewhere. Strands and columns of darkly
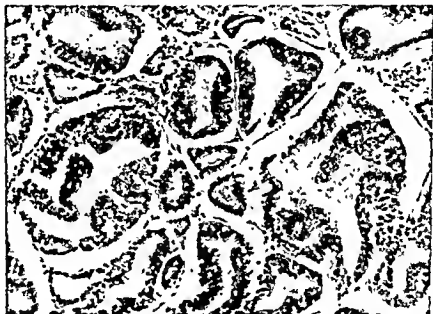
Fig. 274.—Adenocarcinoma of prostate. Atypical new gland formation. × 200.

staining cells infiltrote the glond separated by a dense fibrous stroma. In places the stroma may be so obundant thot no epithelial elements ore visible.

In the odenocarcinomatous variety irregular ocini of large cells ore scattered here and there, the intervening stroma infiltrated with wandering epitheliol cells. The ducts may be distended with masses of cells presenting a certain resemblance to the papillary masses seen in benign hyperplasia, but they lack the supporting stem of connective tissue characteristic of the latter condition (Fig. 274). In rare instances the tumor cells are loaded with lipoid, hoving the foamy appeorance of xanthoma cells, a condition known as *carcinoma xanthomatodes*. In one case which I studied the tumor cells were filled with doubly refractive lipoid not only in the prostate but also in metastases in the lymph nodes, pleural lymphatics, and the greater part of the vertebrol column.

It may be osked by what gross features a carcinoma may be differ-

entiated from a benign overgrowth. The chief points of value are: (1) the different site of the two conditions, (2) the density of cancer compared with the softness or elasticity of adenoma, (3) the hard thick capsule and gritty sensation on cutting and lack of bulging in the case of cancer, (4) the lack of lobulation and dry surface compared with the nodular and moist surface of the hyperplastic prostate.

The *mode of spread* is of great surgical importance. From this point of view, two main types of tumor may be recognized. The first takes the form of a small local lesion, but there is a marked tendency to the formation of widespread early metastasis. In the second there is a massive local lesion, but spread occurs at a later date. Commencing as a rule in the posterior lobe the tumor spreads slowly into the lateral lobes (Fig. 275), but much more rapidly upwards along the line of the ejaculatory ducts,
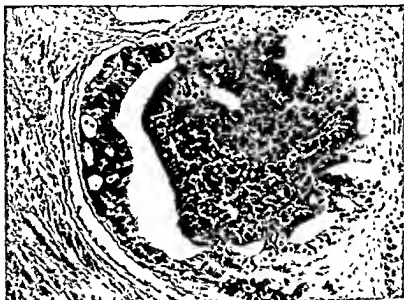
Fig. 275.—Carcinoma of prostate. Malignant cells invading surrounding tissue. × 200

emerging at the upper border of the prostate and passing between the bladder and the seminal vesicles, so that it can readily be felt in this position by the palpating finger in the rectum. Invasion of the trigone with ulceration is usually a later occurrence.

Spread to distant parts may occur through the lymph stream or the blood stream. The pelvic and lumbar lymph nodes are involved early in the disease, and large metastatic deposits are formed there. Lymphatic spread, either by permeation or embolism, may then involve the thoracic and even the supraclavicular nodes, and such organs as the liver, lungs, and pleura may become the seat of secondary growths. There is an abundant nerve supply in and around the prostate, and these nerves are accompanied by lymphatics. Lymphatic permeation as well as lymphatic embolism is common by this route, and serves to explain the very frequent involvement of the bony pelvis and lumbar spine. Sections of the nerves

show them to be surrounded by tumor cells (Fig. 276). Pain is an indication of perineural involvement.

Skeletal metastasis, which occurs in so many cases, must be attributed to blood infection. In this respect the prostate resembles the breast, the thyroid, and the kidney. Kaufmann gives the figures for skeletal metastases as 70 per cent for carcinoma of the prostate, 37 per cent for carcinoma of the thyroid, and 14 per cent for carcinoma of the breast. Another route which may well be responsible for the transfer of tumor cells to the spine is the vertebral system of veins described by Batson (see page 111). These veins pass up from the pelvis inside the spinal canal and receive veins from the vertebral bodies.

In the last few years a new field has been opened up in the study of prostatic carcinoma, bringing it into direct relation with the male sex gland and sex hormone. The story revolves around the enzyme *phosphatase*. For long it has been known that phosphatase is found in abundance in growing bone and cartilage. It is also present in the circulating blood, and in certain of the osteodystrophies, particularly Paget's disease, the level in the blood is markedly raised. Two varieties of the enzyme can be distinguished, a so-called alkaline phosphatase with an activity maximum at pH 9, and a so-called acid phosphatase with an activity maximum at pH 5. The *alkaline phosphatase* is that present in growing bone and apparently produced by osteoblasts; the only conditions in which it is known to be increased in the blood are certain types of bone disease (especially Paget's disease) and liver disease.

Fig. 276.—Perineural spread of carcinoma of prostate. × 450.

The level in the blood may be raised in prostatic cancer owing to bone involvement by metastases. The *acid phosphatase* was originally found in the spleen and kidney of swine and cattle, but by far the greatest concentration is in the prostate where it is apparently produced by the prostatic epithelium. A similarly large amount is found in carcinoma of the prostate. The enzyme can be demonstrated microscopically in the epithelium of both the normal and malignant gland by Gomori's method. It is present in small amounts in infancy and childhood, and is increased during puberty to the high values found in the adult. The increase is due to the influence of androgenic hormones. In cases where the carcinoma is disseminated in the bones, particularly the bony pelvis, there is a marked rise in the acid phosphatase in the serum. Such a rise has been observed in no other condition. Huggins and his associates claim that

when acid phosphatase is present in activity greater than 10 units in 100 c.c. disseminated prostatic cancer is present. In this respect the acid phosphatase test on the blood is comparable with the Aschheim-Zondek test in chorionepithelioma. The increase in the blood is not found in every case.

The development and activity of the prostate are dependent on stimuli from the testes. Castration before puberty prevents development of the prostate, and castration in adult life causes regression of the normal gland and decrease in size in cases of prostatic hypertrophy. Huggins and his associates have applied these facts to the problem of the control of cancer of the prostate with remarkable results. In a series of cases orchidectomy was followed not only by an astonishing improvement in the subjective condition (bone pain, etc.), but also by such objective evidence as a great and permanent fall in the acid phosphatase in the blood, a shrinkage of the primary lesion, and increased density of the metastatic lesions in the roentgenograms. Equally good results are obtained by the use of estrogen therapy (stilboestrol). Both procedures reduce the supply of androgen. Castration eliminates the main source of androgen, while estrogen arrests its output from the testicle by inhibiting the amount of gonadotropin from the pituitary. With either procedure symptoms may return in 7 or 8 months, but some patients have remained symptom-free for two years or more.

That the influence of the testis is androgenic is shown by the fact that injection of androgen in cases of prostatic cancer causes a sharp rise in serum acid phosphatase. Injection of large amounts of estrogen produces a sharp fall in serum acid phosphatase, owing to neutralization of androgenic action.

Sarcoma.—This is a very rare tumor of the prostate. It generally occurs in childhood or early adult life. It forms a soft, rapidly growing tumor. It appears probable that most of the tumors which in the past have been regarded as sarcomas of the prostate are in reality anaplastic forms of carcinoma with little or no cell differentiation. The same holds true for sarcomas of the ovary.

Calculus.—Prostatic calculi, forming in the substance of the gland, are generally multiple and millet seed in size. They give rise to few or no symptoms.

THE URETHRA

The male urethra, which alone will be considered here, is divided into an anterior and a posterior part. The anterior part comprises the penile urethra, the posterior part the membranous and prostatic urethra.

The interior of the urethra does not present a smooth surface, but is indented on all sides by the lacunae of Morgagni, which are depressions in the mucous membrane, and by the openings of the ducts of the glands of Littré. These glands are situated in the roof and walls and to a lesser extent the floor of the anterior urethra. Lying somewhat deeply in the submucosa they form important harboring places for the gonococcus after it has disappeared from the mucous surface. Normally they secret mucus. The epithelial lining of the urethra is columnar in type, but as the result of inflammation it may become pavement or even squamous. The latter varieties present a more formidable barrier to the gonococcus than does the columnar epithelium, and for this reason a second attack is not so intense as the first.

The only common and important pathological condition affecting the urethra is acute inflammation due to the gonococcus, together with the consequences which may result from such inflammation.

GONORRHEAL URETHRITIS

The disease begins as an acute inflammation. By the end of the second day after infection both the lacunae of Morgagni and the glands of Littré are packed with gonococci and pus cells. By the third day extensive invasion of the mucosa has occurred, the columnar epithelium offering little resistance to the gonococcus and soon becoming desquamated. The pavement epithelium of the fossa navicularis, on the other hand, presents an admirable barrier to the inflammatory process.
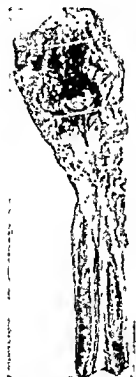
Fig. 277.—Stricture of posterior urethra with hypertrophy of bladder.

Fig. 278.—Urethral calculus which had been present in the penile urethra for 30 years. It consists of two parts.

In course of time the entire mucosa shows the usual signs of inflammation—congestion and the formation of an inflammatory exudate. The process involves the submucosa, and in severe cases may extend as far as the corpora cavernosa. As a rule the inflammation advances slowly up the urethra until the posterior part is involved. The inflammatory process is much more severe in the prostatic than in the membranous urethra, owing to the great number of glands in the former part. There may be an associated inflammation of the prostate, Cowper's glands, the seminal vesicles, and the epididymis.

The ducts of the glands may become blocked, with the resulting con-

version of the glands into pus sacs. In these the gonococcus may linger for considerable periods of time.

The inflammation may clear up in the course of a few weeks. The congestion subsides, the discharge disappears, and the denuded epithelium is replaced, this time, however, by cells of a pavement type.

On the other hand the inflammation may become chronic. The pus sacs already referred to maintain the inflammation, and the mucosa and submucosa are converted into a granulation tissue, at first cellular but becoming more and more fibrous until at last hard scar tissue is formed. The originally elastic and distensible urethra has now become hard and rigid. The sclerosed tissue constitutes an extensive and irregular scar, which contracts and gives rise to a *stricture* of the tube.

Stricture of the Urethra.—This is a narrowing of the channel of the urethra due to the formation of fibrous tissue in the wall with subsequent contraction. It may be inflammatory or traumatic in type.

Inflammatory stricture is usually gonorrheal in origin. It may be single or multiple. The usual site is in the bulb of the urethra, but it may be in any part of the anterior urethra. The gonorrheal inflammation leads to the formation of granulation tissue in the mucosa and submucosa; this is followed by fibrosis and contraction of the scar tissue; finally a very narrow passage may be left, which is readily occluded by transient acute inflammatory edema.

Traumatic stricture is nearly always in the membranous urethra. It is usually due to a fall on the perineum with rupture of the urethra, but sometimes to injury produced by the unskilled passage of an instrument.

The *effects* of a stricture are similar to those of prostatic obstruction. The bladder wall hypertrophies and later the cavity becomes dilated (Fig. 277). There is bilateral hydronephrosis with dilatation of the ureters. The bladder is able to empty itself completely so that, unlike the condition in prostatic obstruction, there is no residual urine. For this reason secondary infection is less likely to occur in obstruction due to stricture. Nevertheless infection is almost certain to occur sooner or later, especially if a catheter has to be passed, and there is danger of an ascending pyelonephritis. Straining helps micturition in stricture, but not in prostatic obstruction.

Congenital stricture due to the presence of a valve-like fold of mucosa in the posterior urethra has already been described under the heading of "Congenital Dilatation of the Ureters."

Calculus of the urethra is a rare condition, usually due to the arrest of a renal or vesical calculus in its downward passage. I once performed an autopsy on a man who died at the age of 78, and who was aware of the presence of a large stone in the penile urethra for at least 30 years (Fig. 278). When he wished to micturate he would push the stone to one side. The bladder was greatly hypertrophied, and both kidneys showed an advanced degree of hydronephrosis.

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CHAPTER XXII

MALE REPRODUCTIVE SYSTEM

The Testicle and Epididymis

The testicle and epididymis may be regarded as one organ. The epididymis is the excretory duct of the testicle. Developmentally, however, they have a separate origin, and it may not be straining analogy too far to compare the male genital gland with the kidney. The kidney develops in two parts, a secreting part and a collecting part; the collecting part, derived from the Wolffian duct, is peculiarly liable to infections either with the tubercle bacillus or with pyogenic organisms, which may reach it by the blood stream or from the bladder, and which may then invade the secreting portion in a secondary manner.

So too the testicle and the epididymis arise separately, the testicle from a mass of fetal tissue lying in front of but distinct from the Wolffian body, whilst the Wolffian duct becomes the duct of the epididymis. The epididymis is the first part of the organ to be attacked by tuberculosis and pyogenic bacteria whether carried by the blood stream or descending from the urethra. This infection may or may not extend to the secreting portion, the testicle.

Enlargement of the testicle may be due, in their order of importance, to inflammation, tuberculosis, syphilis, and neoplasms.

INFLAMMATION OF THE TESTICLE

Inflammation is the commonest disease of the testicle, but it is common in the epididymis and not in the body of the testicle. We may recognize three classes of cases.

1. The inflammation may be practically confined to the epididymis. Gonorrhea is the best example. Tuberculosis at first comes into this category, but later it may spread to the testicle.

2. The inflammation may be confined to the testicle. The orchitis of infections such as mumps, and syphilitic orchitis, belong to this group.

3. The inflammation may involve both testicle and epididymis. Of this traumatic orchitis is an example.

Seeing, therefore, that inflammation tends to be confined to one or other of these parts we may consider under separate heading epididymitis and orchitis.

Inflammation of the epididymis is usually associated with hydrocele, that of the testicle is not, for the dense tunica albuginea by which the testicle is surrounded serves to prevent inflammation extending to neighboring parts.

Epididymitis

There are two main forms of inflammation of the epididymis, the gonorrheal, and the non-gonorrheal. The gonorrheal infection reaches

the epididymis by way of the vas deferens, the non-gonorrheal may follow the same route, or may arrive by the blood stream. Perhaps the last remark is not quite accurate. It is by no means certain that such infections of the epididymis are directly hematogenous. The testicle, it must be remembered, closely resembles the kidney in its development, and may at times assume an excretory function. This serves to explain the not infrequent involvement of the testicle by the organisms of mumps, typhoid, and syphilis. Moreover, the bacteria may fail to find lodgement in the testicle, and may be excreted into the epididymis where they set up a focus of disease. This, probably, is the usual sequence in tuberculosis and may conceivably be the method of infection in gonorrheal epididymitis.

Gonorrheal Epididymitis.—Acute gonorrheal epididymitis is the most frequent complication of gonorrhea, and at the same time the commonest form of testicular inflammation. It is secondary to a posterior urethritis, and occurs in the second and third months of gonorrheal infection.

By whatever route the infection reaches the epididymis the inflammation commences in the lower pole and soon involves the entire organ, although in the milder cases it may be confined to the globus minor. Although it would appear so easy for the infection to spread along the line of the tubules to the testicle, that organ remains entirely free. In this respect the analogy with the kidney breaks down. The cellular tissue around the testicle may, however, become involved in the inflammation, so that the testicle may feel enlarged, hard, and tender.

The type of inflammatory reaction is somewhat peculiar and worthy of note. Definite suppuration occurs, with the formation of minute abscesses containing a few drops of pus, but extensive suppuration with the formation of large abscesses is rare. The entire organ is involved in a widespread inflammatory edema, and is swollen and tender. In the more acute cases an inflammatory hydrocele is a common accompaniment. The spermatic cord may be involved in the inflammatory process, being tender and indurated, but not to any marked degree.

The disease although acute in onset is equally rapid in decline, provided appropriate treatment is employed, and within a few weeks nothing remains but a few tell-tale scars. Scars, however, are things which cannot always be treated lightly, and the fibrosis may be such as to present an insurmountable obstacle to the passage of spermatozoa. Should the condition be bilateral, permanent sterility will result. Usually, however, the inflammation is confined to one side.

Non-gonorrheal Epididymitis.—Inflammation of the epididymis may occasionally be due to pyogenic organisms other than the gonococcus. This is most likely to occur in conditions such as stricture of the urethra or enlarged prostate where a posterior urethritis is apt to develop. Occasionally, however, it develops without such concomitant conditions. In these cases it is secondary to an infection of the seminal vesicles. The causal organism is usually a staphylococcus, but streptococci and Bacillus coli are occasionally found.

The course of the disease is different from that of the gonorrheal cases. The inflammation commences not in the epididymis but in the seminal vesicle, and from there it spreads slowly down in the walls of the vas

deferens. Both the vesicle and the vas become extremely hard and thickened. The speedy resolution of gonorrheal epididymitis is rarely seen in this form. Abscess formation may occur in two places, in the lower pole of the epididymis and in the upper part of the vas at the external abdominal ring. Even after the acute condition has subsided the infection may linger for a long time, so that recurrences are common in contradistinction to their rarity in the gonorrheal variety.

ORCHITIS

Acute inflammation of the body of the testicle is rare compared with inflammation of the epididymis. At the same time it is not an uncommon affection. There are two main groups of causes: 1. trauma; 2. acute infectious fevers. Of these by far the most important is mumps, then come typhoid fever and smallpox, and in a third rare group are many other febrile conditions, too numerous to enumerate.

Traumatic orchitis follows upon a blow on the testicle. The organ rapidly becomes enlarged, but the duration is short, and the condition subsides with equal activity. Atrophy of the testicle may occasionally result.

Metastatic orchitis, due to the formation of a metastatic inflammatory focus, is most typically seen in the case of mumps. The condition develops in about 30 per cent of the cases of this disease. It is usually unilateral, but may be bilateral. Occasionally it may precede the development of parotitis. It is rarely seen before the age of puberty, and is commonest in young men. The testicle is only moderately enlarged, owing to the firm non-elastic tunica albuginea by which the organ is surrounded. The pain is excruciating, and for the same reason. The epididymis is rarely involved. Suppuration is quite uncommon, resolution is the rule, occurring usually by the end of a week. Atrophy is only too frequent, but the testicle may return to a normal condition.

TUBERCULOSIS OF THE GENITAL TRACT

The site of origin of genital tuberculosis is still a matter for discussion with genito-urinary surgeons. The general opinion is that the disease commences in the epididymis, but Young has demonstrated that in many cases, perhaps in most, the primary focus is in the seminal vesicles. From the seminal vesicles the globus minor of the epididymis is generally next attacked, and from the same source the prostate, the urethra, and the bladder may be involved later. The importance of removing the seminal vesicles in any surgical treatment of genital tuberculosis is therefore self-evident.

One point too frequently forgotten must always be kept in mind. Genito-urinary tuberculosis is not an isolated manifestation of the disease. In the great majority of cases tuberculous lesions can be demonstrated in other organs, usually the lungs, and where these cannot be found it may confidently be assumed that they nevertheless exist. From the point of view of treatment, that is of the patient and not merely of the affected organ, this conception is of paramount importance.

In whichever part of the seminal tract the disease may begin the mode of infection must be hematogenous, except in those cases where the bacilli

travel from the kidney down to the prostate. As the pathological changes in the testicle are those which specially attract the attention of the surgeon, chief consideration will be given to them.

Morbid Anatomy.—The lower pole of the epididymis is the first part involved. The disease may remain confined to that part, or it may gradually involve the whole of the epididymis, but particularly the upper pole. At first one and then several nodules are formed, so that the whole epididymis becomes considerably enlarged. In the early stages the nodules are very firm and hard, a characteristic which can readily be recognized on palpation. Sooner or later, however, caseation, softening, and liquefaction occur. Tuberculosis in the genital tract seldom displays the natural tendency to healing which is so marked in the lungs. Even if the infection is not advancing it remains ready to spring into activity at the slightest provocation, and the patient once infected has the sword of Damocles continually suspended over his head. When softening occurs the skin of the scrotum may become adherent to the epididymis, with the formation of a tuberculous fistula. On the other hand softening may not occur, or may be delayed for several years.

Spread to Other Organs.—Tuberculosis does not remain confined to the epididymis. Indeed it is the fact of its early spread to the other parts of the genital tract which makes the determination of the point of onset a matter of so much difficulty. When the patient is first seen by the surgeon, and still more frequently when the parts are examined at autopsy, the epididymis, the vas deferens, the prostate, and the seminal vesicles may all be involved. The path of spread of the infection is a matter of dispute. The obvious route is via the lumen of the vas, but it is more than possible that it is along the lymphatics in the wall of the vas that the bacilli travel. Finally, it must be remembered that if the blood stream has brought infection to the epididymis or seminal vesicles, the other genital organs may be similarly attacked.

The *spermatic cord* is thickened, and hard masses may be felt here and there along its course. Similar nodules are present in the prostate and seminal vesicles. At a later stage these may caseate and soften.

The *tunica vaginalis* is frequently involved, and its inner surface may be found to be studded with tubercles. A hydrocele is the natural consequence, and may have to be tapped before the outline of the testicle can be made out.

The *testicle* itself may escape for a considerable time, but it will not forever remain inviolate. The first part to be involved is the body of Highmore. The fact that the lymphatics of the testicle concentrate at this point suggest that the path of spread may be lymphatic rather than along the seminal tubules. The disease may remain localized to this part of the testicle, or may spread diffusely throughout the organ (Fig. 279).

The condition of *the other epididymis* must be considered in every case. It is a lamentable fact that involvement of the other side is apt to occur no matter what precautions are taken, no matter *how radical* the operative treatment. Once again the route of infection is a matter of discussion. It is improbable that the bacilli pass along the vas in the direction opposite to the normal stream. More likely the spread is by the lymphatics or by a fresh hematogenous infection.
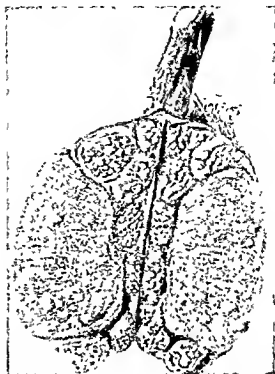
Fig. 279.—Tuberculosis of the testicle. The epididymis is extensively involved, and the infection is beginning to spread to the body of the testicle.
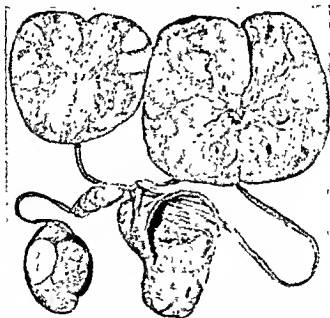
Fig. 280.—Genito-urinary tuberculosis. Involvement of kidneys, ureter, epididymis, testicle, vas deferens, and prostate.

Finally, the infection may spread to *the urinary tract*. From the prostate one or both kidneys may become involved (Fig. 280). A more common occurrence, however, is the downward passage of the bacilli from the kidney to the bladder, with spread to the prostate, vas, and epididymis. About 30 per cent of cases of renal tuberculosis in the male are associated with genital tuberculosis, but the spread is more likely to be downwards than upwards. Still more probable is an independent hematogenous infection of both kidney and epididymis.

SYPHILIS OF THE TESTICLE

Syphilis of the testicle is one of the commonest manifestations of syphilis, but it usually gives rise to no symptoms. It is therefore more frequently seen by the pathologist than by the clinician.

It occurs in two main forms, (1) the gumma, and (2) a diffuse inflammatory infiltration resulting in fibrosis of the organ. Although the former is the more readily recognized, the latter is infinitely the more common. Both forms are usually confined to the body of the testicle, although occasionally the epididymis is involved in the diffuse variety.

A *gumma* forms a hard mass of varying size, producing enlargement of the testicle. At first it is of a greyish-red color, but later becomes more and more white and fibrous. The caseous center and the presence of occasional giant cells at the periphery may lead to confusion with tuberculosis. Softening is uncommon and the elastic fibers in the walls of the tubules are not destroyed as they are in tuberculosis. Antisyphilitic treatment usually produces a remarkable effect upon the gumma, a point of great importance in differentiating the condition from neoplasm. Although the gumma disappears its place is taken by dense scar tissue.

The *diffuse inflammatory form* is probably of frequent occurrence although it does not attract the attention of the patient by the production of symptoms. The testicle is not altered in shape, but in the later stages may be markedly atrophic. It is of a characteristic woody hardness and not only is there an absence of pain and tenderness but the normal testicular sensation is lost. The tunica albuginea is thick and fibrous, and the gland is pervaded with innumerable fine white fibrous bands. These may invade every part of the testicle, or they may be more or less confined to one part. When the normal testicle is cut into, the tubules bulge forward in a characteristic manner. The cut surface of the syphilitic testicle remains perfectly flat, because the tubules are bound down by the abundant fibrous tissue. Should the epididymis be involved it is usually the upper pole which shows the change to the most marked extent, and if enlarged in the earlier stages it may form a helmet-like covering to the body of the testicle.

The *microscopic picture* depends entirely upon the stage of the disease. At first the tubules are separated by a diffuse infiltration of lymphocytes and plasma cells, and spirochetes in abundance can be demonstrated by the Levaditi method. A young connective tissue is formed which becomes more and more fibrous, until finally the testicle may be little more than a mass of fibrous tissue. The cells lining the tubules show a marked degree of fatty degeneration, and become desquamated so as

to lie in masses within the lumen. Eventually the tubules atrophy and disappear.

TUMORS OF THE TESTICLE ·

The subject of tumors of the testicle is a confused and bewildering one, regarding which there is still great difference of opinion. In the older literature they masquerade under many names, such as fibrocystic disease of the testicle, chondroma, chondrosarcoma, round-cell sarcoma, squamous-cell carcinoma, etc. The modern conception of these tumors is a greatly simplified one.

Almost all tumors of the testicle are malignant, and all the malignant tumors cause the excretion of excessive amounts of gonadotropic hormone in the urine. There has been much difference of opinion as to the classification of these tumors, and at the present time there are two main schools of thought. According to the one, represented by Wilms in Germany and Ewing in America, all the testicular tumors are teratomatous in character, arising from primitive germ cells which are totipotent, and can therefore give rise to any form of tissue. In many cases one type of cell proliferats to such a degree that it appears to constitute the entire tumor, so that we have an apparent chondroma, epidermoid carcinoma, etc. The other school, represented by Chevassu in France and by Schultz and Eisendrath in America, consider that not all these tumors are teratomatous, but that some of them arise from the cells of the seminiferous tubules.

Bell made a study of the material in the Edinburgh museums, and found that practically all the tumors fall into two great groups. The first are the germinal cell tumors, the spermatocytoma group, called by Chevassu the seminomas. The second are true

Fig. 281.—Seminoma. × 500

teratomata, the embryomas. These groups appear to be of about equal size.

Seminoma.—These tumors appear to arise from the cells lining the seminiferous tubules, although, as already indicated, Ewing considers that they merely represent a one-sided development of a teratoma or embryonal carcinoma. Appearing in middle life, they are of comparatively slow growth. The seminoma is solid, and the cut surface fleshy and homogeneous, often traversed by fibrous septa which give rise to distinct lobulation. The microscopic picture varies. In some specimens the cells closely resemble the spermatocytes, large in size and with peculiarly clear cytoplasm (Fig. 281). In others the cells are small and contain a large darkly staining nucleus, so that the picture may be indistinguishable from that of lymphosarcoma. A diagnosis of lympho-
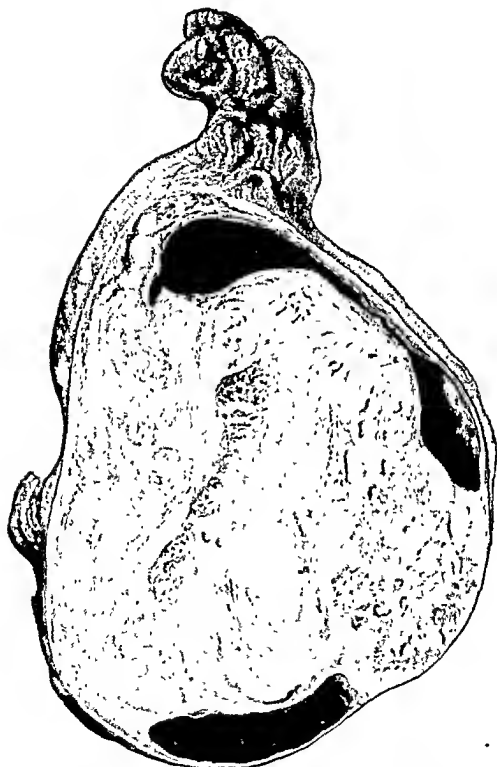
Fig. 282—Embryoma of testicle. The testicle is completely destroyed and replaced by embryonal carcinomatous tissue. There are many small cysts on the right-hand side. A hydrocele is also present. (From Young "Practice of Urology.")

sarcoma of the testicle has often been made in the past. The arrangement of the cells also varies. In the early stages and in the more slowly growing tumors there may be a well marked tubular arrangement, but in the advanced stages and in rapidly growing forms the arrangement may be quite diffuse. On account of this varied picture it is easy to understand how in the past these tumors have been taken for carcinoma in some cases and for sarcoma in others.

Embryoma.—The precise origin of the teratomatous form of tumor is not certain. By Wilms and others it is supposed to arise from one of the ordinary germinal cells by a process analogous to parthenogenesis. It appears more probable that it arises from a germinal blastomere or primitive germinal cell, the progenitor both of the ova and the spermatozoa. These cells are totipotent, so that they produce a teratoid tumor, which may contain structures derived from all three of the primitive layers.

The tumor varies in size from a golf ball up to a fetal head. It often presents a markedly cystic appearance, which earned it the old name of fibrocystic disease (Fig. 282). The cut surface may resemble that of a coarse sponge, or may be finely honeycombed like a colloid goitre. Some of the cysts may be as large as a marble. Parts of the tumor may be solid, and in some specimens there is no cyst formation at all.

The *microscopic* appearance, as might be expected, is extremely varied and composite, for there may be derivatives of mesoblast, hypoblast, and epiblast. From the mesoblast there may be cartilage, bone, plain and striped muscle, fat, and lymphoid tissue. Hyaline cartilage is perhaps the commonest structure. It may be so abundant as to lead to a mistaken diagnosis of chondroma as in Sir James Paget's famous case in which cartilaginous metastases were found in the lungs. The hypoblast is represented by tubular spaces lined by columnar cells, abortive attempts at forming the alimentary canal. The thyroid and other solid glandular organs may be represented. The epiblast is represented most frequently by stratified epithelium, which may show typical cell nests. It will be evident how important it is, when examining one of these tumors, to take a number of blocks from different parts of the specimen, otherwise one may get the erroneous impression of a chondroma, an epidermoid carcinoma, and so on.

An embryoma of the testis may be regarded as innocent in the first instance, but the various elements of which it is composed are so liable to undergo malignant transformation that for practical purposes it may be regarded as a malignant tumor. The growth of one of these elements may so outdistance the others that we have apparent examples of such divers neoplasms as myxochondrosarcoma, adenocarcinoma, scirrhous carcinoma, epidermoid carcinoma, rodent ulcer, dermoid cyst, and chorionepithelioma.

Tumors of the testis, particularly the more embryonal types, respond well to radiation, and the best results are obtained by preoperation radiation. A biopsy should not be done, for the dense tunica forms a natural barrier which, if broken down, will allow the tumor to fungate and spread rapidly. An undescended testis is said to be more liable to malignant change than a normal one.

The *chorionepithelioma of the testicle* is perhaps the greatest curi-

osity in the whole oncology. The tumor is identical in appearance with the similar tumor of the uterus, being red, soft, and hemorrhagic, whilst microscopically syncytial masses of chorionic epithelium are found. The tumor is probably derived from a teratoma, and may be taken to represent a process of specific partial differentiation of pluripotential cells. It is therefore quite different in origin from the chorionepithelioma of the uterus. Secondary growths occur in the lungs and liver. The primary nodule in the testicle is often so small as easily to be overlooked, or it may be destroyed by hemorrhage, a point to be remembered when the point of origin of the secondary masses in the lungs and liver is being sought.

Spread.—All malignant types of tubular tumors are characterized by early metastases in the lymph nodes. The first to be involved are the upper lumbar glands; these may be greatly enlarged, while the primary growth in the testicle is still quite small. The inguinal nodes are not involved until the tumor invades the skin of the scrotum. The tumor reaches the epigastric group, passes along the prevertebral chain to the mediastinum and along the thoracic duct to the left supraclavicular fossa. Above the level of the epigastric nodes metastases from both testes follow the same route. Blood spread to the lungs is particularly characteristic of chorionepithelioma, but it may also occur in other malignant testicular tumors.

The Aschheim-Zondek test is often positive in tumors of the testicle, and provides a clinical test of real value. It appears to be dependent on destruction of the interstitial cells. When the quantitative method is used it is found that the seminoma gives the weakest reaction (500–1500 mouse units per liter of urine), and the chorionepithelioma gives the strongest (over 10,000 mouse units).

UNDESCENDED TESTICLE

The descent of the testicle is accomplished by so complex a mechanism and the distance traversed is so great that there can be little wonder if a hitch should occasionally occur. The testicle may be arrested at any point in its course from the lumbar region to the scrotum, but the usual positions are: 1. in the neighborhood of the kidney; 2. at the internal abdominal ring; 3. in the inguinal canal; and 4. at the external abdominal ring. Of these much the commonest position is in the inguinal canal itself.

Many causes have been assigned for the failure in descent, and it is probable that more than one factor may be responsible. Peritoneal adhesions around the testicle, an unduly small external ring, and a failure in the power of the gubernaculum are amongst the many causes which have been suggested.

Effects.—An undescended testicle, especially one situated in the inguinal canal, is in a position of danger. (1) It is liable to attacks of orchitis due to trauma either in the form of a direct blow or from muscular contraction of the abdominal wall, (2) It is more likely to undergo torsion than the normal testicle, and the effects are more severe. (3) Malignant growth is supposed to be more common in the undescended testicle.

The gland itself early undergoes atrophic changes. The sexual cells disappear and the spermatogenetic power declines, so that an undescended testicle is usually sterile. The interstitial cells, on the other hand, often

appear to be larger and more abundant than usual, and the virile power is retained. In some cases all the parenchymatous cells disappear and only a mass of fibrous tissue remains.

TORSION OF THE TESTICLE

Torsion may occur either in the fully descended testicle or in the undescended testicle. The latter is the more frequent and the more severe. The usual exciting cause is some sudden muscular effort, but cases have been reported which have occurred during sleep. It is commonest in boys and young men.

The twist may occur in either direction and may be from one to four turns. The vessels below the twist are thrombosed, those above it are normal. The tunica vaginalis contains bloody fluid, and the testicle is extremely congested, hemorrhagic, and almost black in color. If the condition is unrelieved gangrene may supervene. Both from its mode of onset and its clinical symptoms torsion of the testicle is apt to be mistaken for strangulated hernia.

HYDROCELE, HEMATOCELE AND VARICOCELE

HYDROCELE

A hydrocele is a sac containing fluid situated within the scrotum. The sac may be the tunica vaginalis, it may form part of the spermatic cord, or it may lie on the surface of the testicle but apart from the tunica vaginalis. Of these varieties the first is by far the commonest.

Hydrocele of the Tunica Vaginalis.—The tunica vaginalis is distended with fluid. This fluid from its composition is evidently inflammatory in nature. The inflammation may be acute and readily recognized, or it may be chronic and of obscure nature. Thus any inflammation of the testicle or epididymis may spread to the tunica vaginalis and give rise to an acute hydrocele. Inflammation of the epididymis is much more likely to behave thus than is inflammation of the testicle. The two infections most often associated with acute hydrocele are gonorrhea and tuberculosis, both of which involve the epididymis rather than the testicle. It may be that the thick tunica albuginea serves to prevent the outward spread of infection from the testicle. Chronic hydrocele may represent the after-effect of the acute form, but in the great majority of cases it comes on insidiously, and no satisfactory explanation for it can be assigned.

We may consider the fluid, the sac, and the effects of the hydrocele.

The *fluid* varies, naturally, as the case happens to be acute or chronic. In the acute form it is moderate in amount, seldom exceeding 3 oz., collects rapidly, and is of varying degrees of turbidity, being in some cases frankly purulent. It contains flakes of fibrin and numerous leucocytes. The fluid in the chronic variety may collect so as to produce enormous distension of the scrotum, is clear, thin, and watery, of a yellow or straw color, neutral in reaction, and with a specific gravity of from 1.020 to 1.025. It contains sodium chloride, carbonates, 6 per cent of albumin, and some fibrinogen, but does not coagulate spontaneously. Occasionally it may present a shimmering appearance due to the presence of cholesterin crystals. In some cases small fibrous bodies may be present, probably

owing to the deposition of salts which become covered with fibrin. Endothelial cells, leucocytes, cholesterin crystals, and sometimes spermatozoa make up the microscopic picture.

The sac may be thin or thick, depending on the acuteness of the condition. In cases of long standing, and especially in those which have been subjected to repeated tapping, an extraordinary degree of thickening may occur. The wall may become as hard as cartilage, and calcareous plates may be deposited in it. Fibrinous adhesions may cause partial obliteration of the sac, and may divide it into compartments. The hydatid of Morgagni

Fig. 283.—Large chronic hydrocele with thick-walled sac. The testicle shows the effects of compression.

may be considerably elongated, and a causal relationship between this and the recurrence of the hydrocele has often been suggested, but the idea is without adequate foundation, for such enlargement may often be found without any accompanying hydrocele.

The *effect* on the testicle may be nil. When, however, the pressure has been severe and prolonged there may be marked thickening of the surrounding fibrous tissue with flattening or atrophy of the gland (Fig. 283). In some cases when the pressure is removed the testicle may return to its original size.

Hydrocele in young people may communicate with the abdominal

cavity owing to an unobliterated processus funicularis, or it may pass for a varying distance along the cord owing to partial obliteration of the processus. The former is called *congenital*, the latter *infantile hydrocele*.

Encysted Hydrocele.—Two fairly common conditions are included under this heading, encysted hydrocele of the epididymis and encysted hydrocele of the spermatic cord. They are, however, very different, and it is regrettable that they should be known by the same name.

Encysted hydrocele of the epididymis, better called *spermatocele,* is a condition of dilatation of the spermatic ducts. It forms a small globular swelling at the upper end of the epididymis, frequently situated between that organ and the testicle. It is quite different from that of a hydrocele, bears no traces of an inflammatory origin, contains hardly any albumin, and is of a peculiar milkiness due to the presence of innumerable spermatozoa. The cyst is usually single, but may be multiple or multilocular.

Encysted hydrocele of the spermatic cord is an entirely different condition. It is merely an unobliterated portion of the processus funicularis lying between the testicle and the internal abdominal ring, which contains a small quantity of clear fluid, and does not communicate with the tunica vaginalis.

HEMATOCELE

A hematocele is a collection of blood in the tunica vaginalis. Other varieties of hematocele have been described to which passing reference will be made. They are of little importance.

The condition is usually associated with a hydrocele, and is due to trauma of some kind. Such trauma may result during the tapping of a hydrocele from mechanical injury to a vein, or the more sudden reduction of the pressure may cause a vein to give way. In other cases a kick or blow is the exciting cause. Occasionally the hematocele may develop without any antecedent trauma. Such cases may be due to the vascularization of an exudate on the surface of the testicle giving way of one of the new-formed vessels, suggesting the somewhat similar mechanism in pachymeningitis haemorrhagica.

The *fluid* is dark, varying in tone from red to brown, and consists of blood mixed with hydrocele fluid. The center of the tunica vaginalis is occupied by a soft breaking-down clot, but the walls are covered with many layers of fibrin, which later become organized and in some cases calcified. Crystals of hematoidin and cholesterin may be found in the fluid.

Other rare forms of hematocele have been described. A hematocele of the cord is merely an effusion of blood into an encysted hydrocele of the cord, or a diffuse effusion into the cellular tissue. A hematocele of the testis is an extravasation of blood between the testis and the tunica vaginalis.

VARICOCELE

Varicocele is a condition of varicosity of the pampiniform plexus, the group of 6 or 8 veins which pass up the cord, and fuse at the internal abdominal vein to form the spermatic vein. As in the case of hydrocele it may be secondary or primary.

The secondary variety is the result of pressure on the spermatic vein, usually owing to an abdominal tumor, especially a tumor of the kidney. It develops rapidly, and the veins do not empty when the patient lies down. In consequence of its etiology it is principally found in elderly men.

The so-called *primary* form is infinitely commoner. We call it primary because no universally accepted cause has so far been assigned for it, although as usual suggested explanations are remarkable for their number and ingenuity. It occurs principally in young unmarried men, and is probably associated with chronic venous congestion consequent upon unrelieved sexual stimulation. In at least 90 per cent of cases it is confined to the left side. The left spermatic vein enters the renal vein at right angles, whereas the vein on the right side enters the inferior vena cava at an oblique angle in the direction of the blood flow. The suction, therefore, is less efficient on the left than on the right. A loaded rectum, moreover, may press upon the left vein.

The veins of the plexus become elongated, tortuous, and give to the palpating finger a sensation suggesting a bag of worms. The dilated veins empty when the patient lies down. Thrombosis is a somewhat uncommon complication, and in cases of long standing a phlebolith may form.

THE PENIS AND SCROTUM

THE PENIS

Phimosis is a common condition in children. The opening of the prepuce is so small that retraction over the glans is impossible. The condition is congenital, and all degrees may be encountered.

Even in the milder forms there is difficulty in urination, and in the course of time this may lead to serious changes in the bladder and kidneys. The bladder becomes trabeculated, and in some cases dilatation of the ureters and hydronephrosis may develop. Preputial stones may form, sometimes in large numbers, owing to the deposition of smegma, epithelial debris, urinary salts, and cholesterin crystals. These stones are small, soft, and brown in color. Occasionally a stone of considerable size may form. A condition of balanitis is often associated with phimosis.

One of the important relationships of phimosis is cancer of the penis. In over 70 per cent of cases of carcinoma of the penis phimosis is or has been present.

Carcinoma is epidermoid in type. It occurs at the usual cancer age, and almost invariably begins either on the glans or on the prepuce. It appears first as a small wart, the nature of which may remain unsuspected for a considerable time. All such warts occurring in elderly men should be regarded with the gravest suspicion, as they are almost certain to prove carcinomatous. Gradually a large fungating cauliflower-like mass is formed, extensive ulceration occurs, and large portions of the organ may be destroyed, with the formation of sinuses communicating with the urethra. The scrotum, testicle, bladder and prostate may become involved. Secondary growths appear first in the inguinal glands, and later in the retroperitoneal groups. Metastases in distant organs occur late in the disease.

Innocent tumors and sarcoma are very rare; as are tuberculosis and gummatous formation.

Tuberculosis is very rare, but I have seen one example of tuberculosis of the glans.
Calcareous deposits may form in old people, causing pain and distortion of the organ
on erection. These deposits may correspond to the formations of true bone found in
some of the lower animals.

THE SCROTUM

Inflammation of the scrotum is due in the great majority of cases to
extension of infection from neighboring structures, especially the testicle.
Occasionally the condition is a primary one, and in debilitated subjects
erysipelas may develop.

Many skin diseases affect the scrotum, but discussion of these would
be out of place here.

In tropical countries *elephantiasis* of the scrotum is a common con-
dition. This is due to lymphatic obstruction from blockage of the lym-
phatics by the Filaria sanguinis hominis. It is the adult worm which pro-
duces the symptoms of the disease. The larvae, the detection of which
in the blood stream by night affords the clue to the diagnosis, apparently
cause no symptoms.

Syphilis is a common affection of the scrotum. A primary chancre may
occasionally occur in this situation. In the secondary stage moist patches
and condylomata are frequent. Later in the disease a gumma may develop.
Much more usual, however, is involvement of the scrotum by an ulcer-
ating gumma of the testicle.

Carcinoma of the scrotum is so similar to carcinoma of the penis in its
general characteristics that it does not call for special description. It is of
course epitheliomatous in type. A point of great etiological interest is its
relation to the irritation produced by the continual presence of soot in
the folds of the skin, so that it has been called chimney sweep's cancer.
It also occurs in workers with coal tar and with paraffin. The condition
is very much more common in England than in America.

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FEMALE REPRODUCTIVE SYSTEM

THE UTERUS

Changes Accompanying Menstruation.—The endometrium is being continually played on by influences from the ovary, and the ovary is acted upon in turn by the pituitary. The ovary produces two hormones, estrin which is formed by the Graafian follicle, and progestin which is formed by the corpus luteum. As the corpus luteum develops from the ruptured follicle, and as rupture of the follicle with discharge of the ovum occurs about the fourteenth day of the menstrual cycle, it follows that the estrin phase corresponds to the first half of the cycle and the progestin phase to the second half. Both of these hormones act on the endometrium producing changes which are readily differentiated under the microscope. As soon as the corpus luteum degenerates (24 to 36 hours before menstruation), the follicular hormone reasserts itself, and probably acts as the direct cause of menstruation.

The endometrial changes may be divided into those of the *interval* or *estrin phase* and the *premenstrual* or *progestin phase* (Fig. 284, A, B, C and D). In the *interval* or *estrin phase*, which lasts from the end of menstruation to ovulation, there is proliferation of tissue to repair that destroyed by menstruation. The endometrium becomes thicker, there is proliferation both of glandular epithelium and stroma as shown by the presence of mitotic figures, the epithelium changes from a low to a high columnar form, and the cells lining the glands may be several layers deep, a condition known as pseudostratification.

The *premenstrual* or *progestin phase* is the stage of glandular secretion and of decidual reaction in the stroma. The epithelial cells become distended with mucin, change from a high to a low type, and finally seem to melt into the mucin which distends the lumen of the glands. As a result of this excessive secretion the glands assume a spirally twisted, cork-screw or saw-tooth appearance, so that buds project into the lumen giving a false suggestion of papillary formation. Meanwhile the oval stroma cells become enlarged, rounded and epithelioid in type, so as to resemble the decidua cells of pregnancy. Shortly before the onset of menstruation the superficial layers become infiltrated with polymorphonuclear leucocytes and mononuclear cells, giving an appearance which is readily mistaken for inflammation. Finally the surface layers undergo necrosis, the walls of the capillaries give way, and menstrual bleeding takes place. It may be noted that menstrual bleeding may occasionally occur apart from ovulation, a condition known as *anovulatory menstruation*. The endometrium remains in the estrin phase. It is commonest at puberty and the menopause, but may occur in the middle of reproductive ⸱⸱⸱

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The changes which have just been outlined are the result of the harmonious action of the follicular and corpus luteum hormones. If ovulation should fail to occur, no corpus luteum will be formed, the second set of

Fig. 284.—The menstrual cycle. A, Interval phase, low power. × 50. B, The same, high power. × 240. C, Premenstrual phase, low power. × 30. D, The same, high power, × 240.

changes will be absent, and the first set will be excessive. This is the condition known as endometrial hyperplasia, which in the past has masqueraded under the name of chronic glandular endometritis.

ENDOMETRIAL HYPERPLASIA

This important gynecological condition is characterized by profuse and irregular uterine hemorrhage, a hyperplastic endometrium, and absence of functioning corpora lutea. Ovulation and the formation of corpora lutea may terminate the disease. Burch and his associates have succeeded in producing endometrial hyperplasia in spayed rodents by the injection of estrogenic hormone, and the condition has been produced in ovariectomized women by the same means. The endometrium may be several centimeters thick, and long polypoid growths may project into the uterine cavity. The *microscopic picture* is one of great glandular proliferation with a complete absence of lutein change and decidual reaction. The glands may be lined by several layers of cells, and there may be some degree of invasion of the muscular wall. The deeper glands may show cystic dilatation, giving what is known as a "Swiss cheese appearance" (Fig. 285). The stroma is abundant, and the superficial layers may show a patchy necrosis, hemorrhage, and infiltration with inflammatory cells. Follicular cysts of considerable size may be present in one ovary, and the other ovary may be shrunken and sclerotic. There is a notable absence of corpora lutea.

Fig. 285.—Endometrial hyperplasia. × 50.

Endometrial hyperplasia is the basis of functional uterine hemorrhage, a condition which is a manifestation of disordered ovarian function and not of any primary lesion in the uterus. The irregular and excessive uterine hemorrhage usually occurs just before or during the menopause, but it may occur in young women. It is peculiarly amenable to treatment, *being benefited by such diverse means as radiotherapy, curettage, and the use of estrogenic hormones.*

ENDOMETRIOSIS

This conveniently non-committal term is used to denote a condition characterized by the formation of endometrium-like masses in a variety of places in the female pelvis and abdominal cavity. As the masses may resemble tumors they are known as endometriomata. The origin of these lesions is a matter of dispute.

It was Sampson of Albany who in 1921 was the first to direct attention to that manifestation of endometriosis which he called endometrial implants. The occurrence of so-called chocolate-colored cysts of the ovary had long been recognized, and lesions of similar structure were found in the recto-vaginal septum and other parts of the pelvis. Sampson suggested that these lesions were due to implantation of living endometrial c "

the surface of the ovary, peritoneum, etc. These cells were supposed to be cast into the cavity of the uterus during menstruation, pass along the tubes, and finally settle and grow at the site of the future lesion. The "implant" consists of gland-like spaces surrounded by columnar epithelium, and separated by the cellular stroma characteristic of the endometrium. Hemorrhage occurs at each menstrual period, so that the lesion contains either fresh blood or blood pigment. When the ovarian cyst ruptures the contents are scattered throughout the pelvis together with more desquamated endometrial cells which set up secondary endometrial implants.

Jacobsen's experimental work served to support Sampson's theory. Uterine curettings from rabbits in heat were sowed in the abdominal cavity, and implants were formed in 83 per cent of the animals. Similar results were obtained in monkeys, the implants being identical with those seen in the human patient.

Sampson's views have met both with support and opposition, the latter especially in Germany, where R. Mayer's theory of the serosal origin of the supposed implants is the popular one. The serosal theory, with which

Fig. 286.—Endometriosis lesions on both ovaries and uterus.

the writer is in agreement, is based on the fact that the entire epithelial apparatus of the female genital tract (endometrium, germinal epithelium of the surface of the ovary, etc.) is derived originally from the primitive peritoneum which forms the epithelial lining of the celomic cavity. As the result of ovarian hormonal stimulus the serosa is believed to revert to its original function and form epithelium-lined cavities. Every pathologist is familiar with the fact that as the result of some stimulus such as chronic irritation the flattened serosal cells in either sex may become cuboidal, invade the underlying tissue, and surround gland-like spaces.

In this connection the occurrence of an ectopic decidual reaction is of interest. A nodular decidual formation in the subserosa of the appendix is common during pregnancy. Similar lesions are found in the ovary, tube, broad ligaments, wall of rectum, etc., i. e., a distribution similar to that of endometriosis. On the appendix the nodules are often mistaken by the surgeon for tubercles. It is evident that under appropriate hormonal stimulation decidual elements may develop from the connective tissue cells which underlie the serosa in the pelvis and lower abdomen. The

mesothelial cells of the surface appear to form the epithelial elements of endometriosis.

The older view that the chocolate-colored blood cysts of the ovary are of follicular origin has been revived by King. It has long been known that some cysts derived from the Graafian follicles, and especially from atretic follicles, may be lined by epithelium which cannot be distinguished from that of the endometrium. This is natural, as the epithelium of both ovary and uterus has a common origin. Rupture of a chocolate-colored cyst may be followed by implants on the peritoneum.

Fig. 287.—Endometrial implants on surface of ovary. (Sampson, in Surg., Gynec., and Obst., March, 1924.)

Fig. 288.—Endometrial implants on terminal loop of ileum. (Sampson, in Surg., Gynec., and Obst., March, 1924.)

It is important to realize that the idea of normal adult tissues becoming implanted in other organs and growing there so as to produce irritation is quite without precedent in the science of pathology. It should be realized that transplantation is not necessary to account for the presence of a tissue at a distance from the normal site of that tissue. Metaplasia will give the same result.

These objections are raised not with the idea of discrediting Sampson's theory and the brilliant work by which it has been supported, but in order to bring home the truth that it is still a theory, and not a fact as many

gynecologists seem to imagine. It is possible that some of the lesions may be endometrial in origin, some serosal, and some ovarian.

The occurrence of the lesions is confined to the active reproductive period of the patient's life. Removal of the ovaries may be followed by atrophy and disappearance of the lesions. They are said occasionally to undergo malignant change, and Sampson believes that some of the malignant cystadenomas of the ovary arise in this way.

The *lesions* are most often seen in the *ovary*, where they form one variety of ovarian hematoma, and are commonly known as *chocolate-colored cysts* (Figs. 286, 287). The cysts, which are close to the surface, are quite small, are lined by columnar epithelium, and are separated from one another by the highly cellular stroma so characteristic of the endometrium, in which are embedded many small glands like those
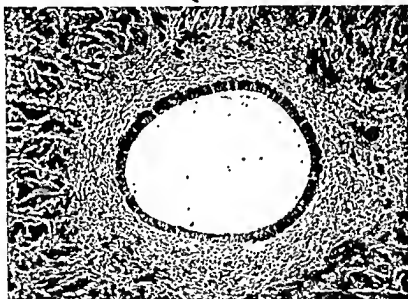
Fig. 289—Adenomyosis of uterus. Around the glandular space there is the characteristic endometrial stroma, surrounded in turn by the muscular wall of the uterus. × 100.

of the uterus. There is no plain muscle in the ovary, but in the other lesions this is commonly present. The contents are hemorrhagic, and the blood is renewed at each menstrual period. Rupture of the cysts and liberation of the blood may be followed by the formation of peculiarly dense adhesions which in the past have been naturally thought to be inflammatory in nature.

Similar lesions may occur in the recto-vaginal septum. The dense and hard adhesions may be mistaken for d'malignant growth in this region. Endometriomata may occur in the Fallopian tubes, the broad and round ligaments, the appendix, the wall of the intestine (Fig. 288), the umbilicus, the groin and in abdominal scars after operations on the uterus. Lesions of the bowel wall may produce obstruction, which may simulate that of carcinoma, a very important clinical point. The obstruction may be worse at the menstrual period. Blood may be discharged from an umbilical

endometrioma at the menstrual period. Endometrioma of the groin is particularly puzzling. Here the mechanism cannot be that of endometrial implantation. Sampson has shown that endometrial tissue may be found within lymphatics and venous sinuses, and suggests that the cellular masses may spread in the same way as carcinoma, *i. e.*, by the lymph and blood stream as well as by the natural passages (tubes). An inguinal endometrioma may therefore be due to lymph spread. Or it may arise from the remains of an embryological peritoneal process in the inguinal canal, the processus vaginalis (serosal origin).

Adenomyosis.—In this condition there is an intermingling of glandular and muscular elements (Fig. 289). It is not a true tumor, so that the term adenomyoma, formerly applied to it, is a misnomer. Von Recklinghausen believed that the epithelial elements of the lesion arose from portions of the Wolffian body which had become separated in early fetal life, but Cullen showed by means of serial sections that there was direct continuity of epithelium between the lesion and the endometrium. Areas of decidua have been found in the lesion shortly after labor, and even in cases of tubal pregnancy. Although the lesion is sometimes spoken of as a variety of endometriosis, it will be apparent that the relation of the two conditions is merely casual and in no way intimate. Adenomyosis consists of and is derived from endometrium, but in endometriosis the new tissue is more probably of serosal origin.

The *gross appearance* is usually characteristic. The lesion may be limited to the anterior or posterior wall or may form a mantle just outside the mucosa. Although the uterus may be enlarged to two or three times its normal size, and the affected part may be markedly thickened, the normal outline of the organ is usually retained. When the uterus is opened the diagnosis can often be made from the gross appearance. The anterior or posterior wall is diffusely thickened, with a complete absence of the sharp demarcation so characteristic of the ordinary fibroid. The thickened portion of muscle is coarsely striated, and homogeneous translucent areas resembling mucous membrane may be scattered through it. These areas often present a brownish discoloration due to the presence of extravasated menstrual blood. Small cystic spaces filled with chocolate-colored contents may be scattered throughout these mucosal areas. The line of demarcation between the lesion and the normal mucous membrane is always sharp; it extends to, but never into, the endometrium.

Microscopically, the growth is made up of fibromyomatous tissue, only differing from that of an ordinary fibroid in that it is not encapsulated, together with glandular structures. The latter resemble the normal endometrium, although not so regular in appearance. "The uterine mucosa is often of normal thickness and looks perfectly normal, but as we approach the underlying diffuse myomatous tissue the mucosa is seen to penetrate it in all directions, sometimes as an individual gland, but often large areas of mucosa are seen extending into the depth. In favorable sections one can follow a prolongation of the mucosa half way through the uterus" (Cullen).

Interstitial Endometrioma.—In endometriosis the dominant element is epithelium. Occasionally the interstitial cells of the endometrium assume invasive qualities under the influence, apparently, of hormonal stimula-

tion. Under normal conditions root-like strands of these cells penetrate for a short distance into the muscularis. As the result of abnormal stimulation this invasion may become almost sarcomatoid in its character and form a tumor-like lesion known as interstitial endometriosis (Goodall). The interstitial cell is in a constant state of flux during the sex life of the individual, and it has a high potentiality for differentiation, so that the mass may resemble a sarcoma (soft) or a fibroma (hard) in both gross and microscopic appearance. Undoubtedly in the past this condition has frequently been diagnosed pathologically as sarcoma. An unique feature presented by some of these tumors is the presence on the cut surface of hundreds of worm-like masses occupying either lymphatics or veins. In one case with which I am familiar the patient is alive and well four years after removal of the uterus, although long strings composed of masses of interstitial endometrial cells could be pulled out of the veins of the uterine wall.

ENDOMETRITIS

Inflammation of the uterus may affect the endometrium (endometritis), the uterine muscle (metritis), the peritoneal covering (perimetritis), or the neighboring cellular tissue (parametritis).

Acute Endometritis.—This may occur in the pregnant or the non-pregnant uterus. The former, known as puerperal sepsis, is by far the more important and common, and will therefore be described in detail. The chief cause of inflammation in the non-pregnant uterus is the gonococcus. Other conditions which may give rise to it are necrotic submucous fibroid, an ulcerating carcinoma, the passage of dirty instruments, etc.

Puerperal Endometritis.—The puerperal uterus readily lends itself to infection. When bacteria are introduced into the healthy non-pregnant uterus they are speedily disposed of. In the puerperal uterus, however, there is a large raw surface, and, still more important, there are fragments of tissue deprived of their blood supply and waiting, as it were, for infection. This infection may be by saprophytic organisms, of which Bacillus proteus is an example, in which case a condition of sapremia results. The infection is local, but the poisons produced in the decomposing mass are absorbed and give rise to poisoning of varying degrees of intensity.

In the great majority of cases the invading bacteria are streptococci, which may be aërobic or anaërobic. *Aërobic hemolytic streptococci* are the cause of the majority of severe infections. Lancefield and Hare have divided hemolytic streptococci into 4 groups by means of precipitin tests; these groups they named A, B, C, and D. The important fact soon emerged that only group A is responsible for human infection, and that this group constitutes only a small proportion of the hemolytic streptococci in the nose and throat of man. Group A is not found in the vaginal canal before labor, but in puerperal sepsis of severe type it is the principal infective agent. It would appear, therefore, that it is transferred to the vaginal canal of the patient from the nose and throat either of the patient or, more probably, of some one attending the patient, either doctor or nurse. It was in 1910 that Schottmüller first called attention to *anaërobic streptococci* as a frequent cause of puerperal sepsis, but it was *only* after a quarter of a century through the writings of Schwarz and Brown and other workers that their significance came to be fully realized. These

anaërobic organisms are present in the vaginal canals of 40 per cent of women at term. They get their chance when labor is prolonged and the tissues are bruised. The infection is of a less severe type, less likely to be fatal, as anaerobic streptococci are generally non-invasive saprophytes, but under favorable conditions such as the presence of thrombi in the uterine veins they may reach the blood stream with fatal results. The infection is endogenous, in comparison with the exogenous infection by aërobic streptococci. Its prevention therefore presents a more difficult problem.

The uterus is soft, flabby, and enlarged. The cavity is lined with ragged, greenish-black, decomposing tissue which may or may not have a putrid odor. Under this layer of necrotic tissue, fibrin, and bacteria there is a protective zone of leucocytes. In cases of sapremia this zone is wide and sufficient to prevent invasion of the deeper tissues, unless it be broken down by injudicious and violent curettage. Deeper still the muscular tissue is edematous but free from bacteria. In streptococcal septicemia, on the other hand, the protective zone is thin and poorly formed, and the organisms can be seen invading the deeper muscular layers (Fig. 290). It is essentially a spreading condition.

The extension may take many forms. The invading bacteria may penetrate the muscular wall, infect the serous coat, and set up a peritonitis, at first local, but soon becoming general. Or the broad ligament and neighboring tissue may become infiltrated with the formation of large abscesses. Or the infection may pass along the Fallopian tubes and thus reach the peritoneal cavity with disastrous results. Finally distant parts may become involved by infection through the lymphatics or the blood stream. Septic thrombophlebitis occurs, and the veins are represented by great gaping

Fig. 290.—Streptococci invading lymph spaces. × 500

channels filled with infected thrombi, which are at first firm, but soon become converted into foul necrotic débris similar to that lining the cavity, or into actual pus. This material is swept into the blood stream, and forms pyemic abscesses throughout the body, in the lungs, kidneys, joints, etc. (Fig. 291). The valves of the heart are frequently infected, and an ulcerative endocarditis adds to the gravity of the picture. Such is the course of a septic endometritis in its most terrible form.

Pelvic Cellulitis (Parametritis).—This is a term commonly used by gynecologists. Cellulitis signifies an inflammation of connective tissue due

to a wound infection. Pelvic cellulitis may result from infection of lacerations of cervix and vagina occurring during parturition or abortion or from surgical operations on the cervix. It frequently occurs in conjunction with carcinoma of the cervix. Infection reaches the pelvic cellular tissue either by lymphatics or direct continuity of tissue. The common infecting organism is the streptococcus. Infection spreads in the retroperitoneal fascial planes and there may be abscess formation. While the condition may be a long-drawn-out one, resolution is usually complete and no impairment of reproductive function results.

Fig. 291.— The spread of puerperal infection by the blood stream. (Maitland, Amer. Jour. of Surg., Vol. 26, 1914.)

Cervical Endometritis Cervical Erosion.—We have already seen that the cervical mucosa, which reflects only minor changes during menstruation, differs in some important particulars from that of the body. It also behaves differently in response to chronic irritation.

Although the term cervical erosion is in everyday use, the condition is in no sense a true erosion, for no raw surface is produced. It is instead a condition of overgrowth of the mucosa of the cervical canal, which displays a tendency to extend its normal limits on to the vaginal portion of the cervix. As the columnar epithelium of the canal has none of the opacity

of the dense stratified epithelium of the vagina, the affected area of the vaginal part of the cervix has a red and eroded appearance.

The external os appears red and patulous, and the mucosa is swollen. The line of division between the cervical canal and that part of the cervix covered with stratified vaginal epithelium is no longer sharply defined, and a red patch may be seen on the surface of the vaginal portion. In some cases the small bluish swellings called Nabothian follicles are very evident.

The commonest causes of erosion are laceration of the cervix in child-birth and gonorrheal infection of the cervix.

In the former case if the tear be a superficial one it is covered by the vaginal epithelium and no harm is done. If, however, it is deep, there is a tendency for the lips of the cervix to become everted, so that the bright red mucosa of the cervical canal becomes exposed to view. Infection is superadded, and the resulting fibrosis still further increases the eversion.

Fig. 292.—Endocervicitis showing distended glands.

At the same time there is a tendency for the cylindrical epithelium to extend on to the vaginal aspect of the cervix and replace the normal stratified epithelium. Owing partly to the infection, partly to the irritation from exposure, the epithelium of the canal, both on the surface and in the glands, proliferates, so that the surface epithelium becomes thickened and the deeper parts present a glandular appearance.

A somewhat similar condition may result from gonorrheal infection. The cervix is thickened and edematous, and once more the mucosa of the cervical canal begins to protrude through the external os. Glandular proliferation and replacement of the stratified by the columnar epithelium proceeds as before.

Microscopic Appearance.—The mucosa is seen to be packed with small rounded cells, particularly in the subepithelial tissue and around the glands. The glands themselves are stimulated to activity, proliferate, secrete an abundant supply of mucus, and become distended (Fig. 292).

The surface may be covered with papillary projections, each covered by a single layer of columnar epithelium. After a time the squamous epithelium may once more grow over the red patch, or it may be that the columnar becomes converted into squamous epithelium. This process is known as "healing" of the erosion. This new thick epithelium tends to close the mouths of the ducts of the glands, and as at the same time the stroma becomes more and more fibrous and tends to block the ducts, the glands become dilated into Nabothian follicles, which may attain the size of a pea or even larger.

Chronic Metritis.—For many years it has been taught that one of the chief causes of irregular uterine hemorrhage about the time of the menopause or shortly before it is the condition known as chronic metritis or fibrosis uteri. The anatomical basis of the condition was said to be an increase of elastic tissue and fibrous tissue in the myometrium which was supposed to interfere with the muscular contractions, which in turn controlled menstrual bleeding. The elastic tissue increase was thought to be due to subinvolution, itself the result of a chronic metritis of the myometrium (chronic metritis). This conception has gone the way of other gynecological shibboleths. In the first place there is no evidence that muscular contractions have anything to do with the regulation of menstrual bleeding, although undoubtedly they play an important part in the control of hemorrhage after labor. In the second place there is nothing to suggest that the presence of elastic tissue in the uterine muscle bears any relation to hemorrhage. After each puerperium there is a very definite increase in the elastic tissue of the uterine wall, so that a multipara may show much elastic and fibrous tissue at the time of the menopause. With increasing age collagen fibers increase in the uterine wall and replace the muscle. It is most probable that here, as in endometrial hyperplasia, the bleeding is due to ovarian dysfunction. As there is no evidence of inflammation in the uterus, the term chronic metritis should be finally dropped.

Syphilis of the Uterus.—Syphilis of the uterus is essentially syphilis of the cervix uteri. Although the condition is rare it is of practical importance because it may readily be mistaken clinically for carcinoma of the cervix. The lesion may either be a chancre or a late gummatous lesion. There is no difficulty in differentiating cancer of the cervix from syphilis under the microscope. In a primary sore Spirochaeta pallida can be demonstrated both in smears and in sections of the tissue.

FIBROID TUMORS OF THE UTERUS

The commonest tumor in the body is the myoma, fibromyoma, or fibroid tumor of the uterus. Of all women between the periods of puberty and the menopause 1 in 5 have fibroids of the uterus, and in the black races the proportion is said to be as high as 1 in 2 or even 1 in 1.

The age incidence is very definite. These tumors are almost entirely confined to the period of reproductive activity. Their exact cause, like that of all other real tumors, is of course unknown, but the relation of the internal secretion of the ovaries, on which the reproductive activity of the uterus is entirely dependent, must be taken into account.

Morbid Anatomy.—A fibroid of the uterus is a true myoma, the type cell is a plain muscle cell, but the proportion of fibrous tissue is often so great that it may with justice be called a fibromyoma. The tumor originates in the uterine wall, usually in the body; in 8 per cent of cases in the cervix. It is rarely single, and often large numbers are present (Fig. 293).

The gross appearance of fibroids is very variable (Fig. 294) depending largely upon the various degenerations to which they are liable. In an uncomplicated case the tumor is hard, of a glistening white color, and presents an appearance of numerous whorls not unlike that of the surface

of a ball of wool. The more fibrous tissue it contains the more white and glistening it is. Subserous fibroids are the most fibrous, submucous the most muscular. The hard white tumor is sharply demarcated from the surrounding softer and more reddish-brown muscle, and a very definite capsule of compressed muscle tissue is formed from which the tumor may as a rule be readily shelled out. The capsule is highly vascular and supplies the tumor with blood. The larger the tumor, the further will its center be from the blood supply and the more liable to degeneration.

The *microscopic appearance* is one of interlacing bundles of plain muscle fibers, some cut longitudinally, some transversely, separated by

Fig. 293.—Fibroids of uterus. *Multiple tumors of varying size causing great enlargement of the uterus.*

a varying amount of fibrous tissue (Fig. 295). The small tumors consist almost entirely of muscle fibers, but the larger and older varieties may be largely composed of fibrous tissue. As a rule the blood vessels are few and thin-walled. The readiest means of distinguishing the muscular from the fibrous tissue is by means of a connective tissue stain (van Gieson, Mallory, Masson) which stains muscle fibers one color and collagen tissue fibers another. Of course if fibroblasts are numerous they also will take on the yellow stain. The nuclei of the muscle cells, however, are shorter and plumper, whereas those of the fibrous tissue cells are more slender and spindle-shaped. Degeneration will change the picture (Fig. 296).

or cystic, owing to their fairly efficient blood supply, but they are liable to the red degeneration of pregnancy.

The *subperitoneal fibroid* commences as the interstitial variety and later becomes subserous by being extruded through its capsule. These tumors are usually multiple and may attain an enormous size. They may be attached to the uterus in a sessile manner, but frequently there is a well developed pedicle which in some cases becomes extremely attenuated. The tumor derives its blood supply through the pedicle, and it is evident that a slight degree of torsion or pressure on the pedicle may interfere seriously with the supply of nourishment. For this reason hyaline and cystic degeneration is much more frequent than in the other two varieties. As a rule subperitoneal fibroids are remarkably free from adhesions, but occasionally it happens that connections are established with
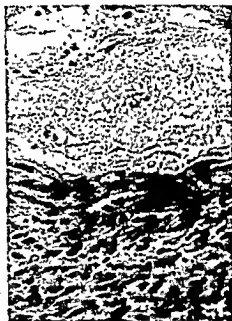
Fig. 295.—Fibromyoma of uterus. × 120.

Fig. 296.—Myoma of uterus showing mucoid degeneration. × 300.

surrounding structures of which the most important is the omentum. In this way the tumor acquires a second source of blood supply, which, in the rare cases where the attachment to the uterus is severed, becomes the only source. To such tumors the name parasitic fibroids is given. When the abdomen is opened in these cases of omental attachment the appearance may be very striking, for not only are the epiploic vessels much enlarged but the lymphatics may be greatly distended, so that the surgeon sees the dark red color of the arteries, the deep blue of the veins, and the pale yellow of the distended lymphatics. In subperitoneal fibroids the muscle is often almost entirely replaced by fibrous tissue in which, as has already been remarked, degenerative changes are of frequent occurrence.

The *submucous fibroid* is naturally the variety most likely to produce symptoms, even when quite small in size. The tumor is usually single, but in some exceptional cases the cavity of the uterus may be crowded

with numerous small tumors, the contiguous surfaces of which may be faceted like multiple calculi in a gall bladder. Owing to the uterine contractions the fibroid tends to become more and more polypoid, until finally it may be extruded into the vagina. Complete spontaneous separation of the pedicle is a very rare event. The submucous fibroid has escaped from its capsule and is covered only by the endometrium, from which it derives the greater part of its blood supply. When extruded through the external os its surface is peculiarly liable to ulceration and infection, and sloughing of the entire tumor may occur. Occasionally, however, the epithelium of the investing endometrium may become thickened and squamous in character, although remaining columnar in the glands. A soft,

Fig 297.—Large fibroid of cervix uteri. The uterus is perched upon the top of the tumor.

submucous fibroid gradually enlarging and distending the uterus may closely simulate a pregnancy, and even when the abdomen is opened it may be almost impossible to differentiate the two conditions. To add to the difficulty a corpus luteum of considerable size may be present in one of the ovaries. When the cavity of the uterus is occupied by a fibroid the endometrium is occasionally thickened, and there may be extensive hemorrhage in the stroma. Similar changes, although to a lesser extent, may be present in some interstitial fibroids. They are responsible for the menorrhagia characteristic of the disease.

Cervical Fibroids.—From 6 to 8 per cent of fibroid tumors occur in the cervix (Fig. 297). The tumor is always single, although it may be

associated with fibroids of the body of the uterus. It may be *interstitial,* arising usually from the posterior wall, at first spherical but later oval, and growing upwards with the body of the uterus perched as a small mass on the summit of the tumor.

Or it may be *subperitoneal,* in which case it grows out into the broad ligament, and produces great distortion, flattening, and elongation of the uterus. The dangers of cervical fibroids, should the patient become pregnant, need no emphasis (Fig. 298).

Degenerative Changes.—Fibroid tumors, particularly those of the subperitoneal variety, are peculiarly liable to degenerative changes.

Atrophy may occur after the menopause, due probably to the withdrawal of the ovarian stimulus. A similar result may sometimes be ob-
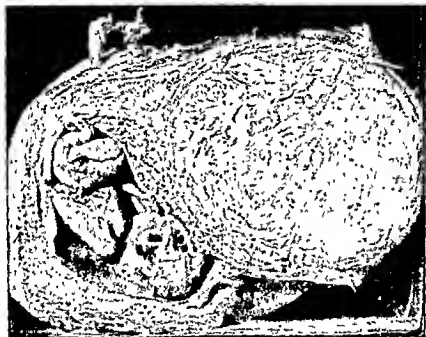
Fig. 298.—Fibroid of cervix complicating pregnancy. The impossibility of delivery is very evident.

tained by removal of the ovaries. The tumor cells lose their power of reproduction and die.

Hyaline degeneration is perhaps the most frequent change, due to insufficiency in the blood supply. It is therefore most frequent in subperitoneal tumors with narrow pedicles. The collagen fibrils become converted into a series of interlacing trabeculae of homogeneous appearance, and stain deeply with eosin and fuchsin. The muscle fibers atrophy and may largely disappear.

Cystic degeneration is a sequel of the hyaline change. The hyaline material becomes liquefied, and numerous cyst-like cavities are formed. These are not true cysts, for they possess no epithelial lining. Moreover the fluid contents, although often highly albuminous, give no reaction for mucin, or pseudomucin. The fluid is usually straw-colored, but may

tinted darkly with blood. There may be numerous small cysts or one large cavity.

Fatty degeneration occasionally appears about the time of the menopause. The tumor loses its whorled appearance, and the cut surface is homogeneous and of a yellow color. The muscle fibers are replaced by rows of small fat droplets staining red with Sudan III or Scharlach R. The importance of the condition lies in the fact that it is the usual precursor of calcification.

Calcareous degeneration is occasionally met with in elderly patients, and may readily be recognized by means of the X-rays. Subperitoneal fibroids are the most frequently affected. The change is preceded by fatty degeneration. The fat is broken up into glycerin and a fatty acid, and the
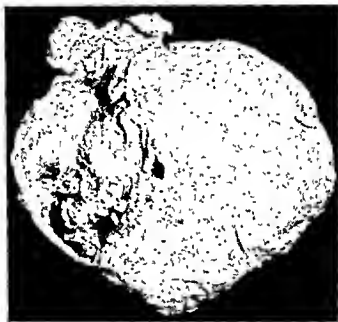
Fig. 299.—Sarcomatous degeneration of a uterine fibroid. The cut surface has completely lost its striated character and is now quite homogeneous.

latter unites with the calcium in the blood to form an insoluble soap, which in turn is converted into the carbonate and phosphate of calcium. Sometimes the entire tumor is calcified, sometimes only the outer shell.

Red degeneration is a peculiar change characterized by the sudden onset of pain and tenderness in the tumor. The fibroid, which is usually quite soft, varies in color from a pink to a mahogany-brown, and on section has been likened to a raw beefsteak. The condition is usually associated with pregnancy, but cases have been recorded in spinsters at the menopause. The degeneration is a rapid necrosis due to the action of autolytic ferments converting insoluble tissue into a soluble form. A peculiar fishy smell is given off, owing to the formation of decomposition products. The red color, which is merely incidental, appears to be due to hemolysis from the lipoid substances produced. On the other hand,

thrombosis of the veins is often a prominent feature, and it has been suggested that the condition may be analogous to a red infarct. This type of degeneration may occur in any variety of fibroid, but is most frequent in the interstitial form.

Sarcomatous Degeneration.—Sarcomatous metaplasia occurs in from 1 to 2 per cent of uterine fibroids. In a well marked case the condition is readily recognized from the gross appearance, for the sarcomatous part is sharply differentiated from the surrounding fibroid. It is soft, much yellower than the white tissue of the fibroid, and the surface is homogeneous instead of whorled (Fig. 299). Degeneration cysts may be present. The malignant change commences in the part of the fibroid furthest from the blood supply, that is the center. The earlier stages cannot be recognized by the naked eye, and need the microscope for their detection.

The malignant metaplasia may affect either the fibrous tissue or the muscular tissue elements of the tumor. Thus we may speak of a fibrosarcoma and a myosarcoma, although strictly speaking the term myosarcoma is inaccurate, for a true sarcoma arises only from connective tissue. In both cases the cells and their nuclei are large, and have an appearance of active growth; mitotic figures are common. The last-named is the most important single factor in determining the presence of malignancy. It is evident that in some cases it will be extremely difficult to determine whether or not the condition should be regarded as malignant.

CANCER OF THE UTERUS

The uterus is one of the organs most frequently affected by carcinoma. Cancer of the uterus and cancer of the breast are of about equal frequency. It is commonest between the ages of 45 and 55, at a time when the uterus is undergoing involutionary changes. The cervix and body of the uterus differ in several respects, both anatomical and functional. It is natural, therefore, that cancer of the body and cancer of the cervix are two distinct diseases.

CANCER OF THE CERVIX

Cancer of the cervix is much commoner than cancer of the body and much more fatal. Over 90 per cent of cases occur in women who have borne children, and it is noteworthy that the fecundity of patients who eventually develop this form of cancer is above the average. Laceration of the cervix is a frequent antecedent. These facts form the basis for the confident assertion that injury to the cervix is the most important etiological factor. Although this dogma has been accepted for many years, it seems time to call it in question. In no other part of the body does a single laceration, even though followed by infection, act as a carcinogenic agent. It is now known that the epithelium of the cervix is subject to hormonal stimulation, and it is possible that this may be a factor of greater importance than trauma. Gardner and his associates have produced cancer of the cervix in mice by injections of estrogens, although they failed with the guinea pig and monkey. The highest incidence of female genital cancer occurs at or after the menopause when ovulation has stopped. There is therefore no corpus luteum hormone, but the output of estrogen may continue, especially if the ovaries are cystic. Carcinoma of the cervix may

occur in women who have been delivered by Caesarian section, and in whom there can be no question of laceration of the cervix. In one case with which I am familiar carcinoma developed ten years after delivery by section. It is evident that hormonal imbalance must be considered as a possible agent in the etiology of female genital cancer. The disease commences in a very insidious fashion, and is usually well advanced before a diagnosis is made.

In 1928 Papanicolaou introduced a method of diagnosing uterine cancer by examining the cells of a vaginal smear. The material is aspirated, blown on to a slide, fixed before being allowed to dry, and stained. Correct interpretation of the microscopic picture is not easy and demands considerable experience. A positive result indicates that a confirmatory biopsy should be performed. In 127 cases of cervical cancer a correct diagnosis was made in 123 by Papanicolaou and Traut.

Fig. 300.—*Carcinoma of cervix.*

Gross Appearance.—As in the stomach, the lip, and other positions, cancer of the cervix may take one of three forms:

1. It may extend on the surface, forming a large, fungating, cauliflower-like mass which projects into the cavity of the vagina. This variety usually arises from the lip of the external os, and shows little tendency to invade the deeper tissues. Ulceration occurs readily, and hemorrhage especially after coitus is an early symptom.

2. It may extend deeply in the direction of the internal os, causing enlargement of the cervix as a whole, and eventually producing a deep ragged cavity, lined with crumbly sloughing débris which bleeds at a touch (Fig. 300). This is the commonest and at the same time the most malignant form, giving rise to widespread infiltration of the surrounding tissues and early involvement of the lymphatic glands.

3. The least common form is that in which a flat indurated ulcer is produced which tends to spread superficially, and is of comparatively slow growth. It is found chiefly in elderly patients.

Microscopic Appearance.—Two types of epithelium are found in the cervix. The vaginal portion (portio vaginalis or simply portio) is covered by stratified squamous epithelium of the epidermal type, while the cervical canal is lined by a single layer of columnar epithelium. Corresponding to these two types of epithelium we find two types of tumor, a common epidermoid carcinoma, and a rarer adenocarcinoma which forms less than 4 per cent of the total. But it is not safe to conclude that the former must arise from the portio and the latter from the cervical canal, for squamous epithelium may extend into the canal, and the racemose glands of the portio may be the starting-point of an adenocarcinoma.

It seems probable that in the majority of cases the tumor originates at the external os which has been the seat of a cervical erosion with change from a squamous to a columnar type of epithelium and reversion again to a squamous type with gradual development of an epidermoid carcinoma. Columns of cells grow down into the deeper tissues, usually showing numerous mitotic figures.

Gynecologists have made minute subdivisions according to the type of cell (spinous, transitional, spindle, etc.) in the hope that the radiosensitivity of the tumors might be determined, seeing that radiation therapy plays such an important part in the treatment of the condition. It seems better to speak merely of the degree of differentiation which the tumor exhibits. The cases of epidermoid carcinoma may be divided into three groups according to their degree of differentiation, and these groups show a corresponding variation in degree of radiosensitivity (Healy and Cutler). Group 1 (20 per cent) is the *adult type*, made up of highly differentiated cells with a tendency to cornification and the formation of pearls. It is radioresistant. Group 2 (60 per cent) is the *plexiform type* (Fig. 301) in which the cells have lost most of their squamous character, show a plexiform arrangement, a tendency to infiltration, and a moderate degree of anaplasia. The tumor is more radiosensitive. Group 3 (20 per cent) is the *anaplastic type* in which the cells have lost all squamous characters, are completely undifferentiated and diffusely invasive. They are highly radiosensitive. When the results of radiation therapy are analyzed the curious position is revealed that the best results (permanent cure) are obtained with the most malignant tumors, *i.e.*, those of Group 3. The
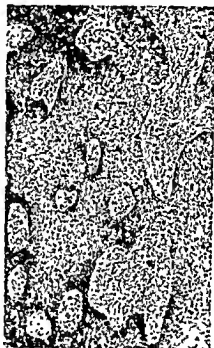
Fig. 301.—Carcinoma of cervix, plexiform type. × 80.

reverse is the case when the growths are removed surgically. This at least is the commonly held view, but it is open to question and the matter cannot be regarded as settled. The rather uncommon adenocarcinoma seems to be less invasive than the epidermoid form, so that the operative results are more favorable, but it is less radiosensitive.

It is important for the pathologist to realize that cancer-like lesions may occur in the cervix which may suggest epidermoid carcinoma or adenocarcinoma, but are essentially innocent. Invading epithelial strands may suggest cancer under the low power, but high power examination shows that the cells are uniform in form and appearance, there is no hyperchromatism and no mitosis. As mitosis is so common in cancer of the cervix, its absence should arouse suspicion. The condition is really an example of benign epithelial invasion.

Spread.—The malignancy of cancer of the cervix is due to its invasive character. The local condition may be readily removed, but only too often the surrounding tissues have already become infected. The spread may be (1) by lymphatic spaces, (2) by lymphatic vessels, or (3) by the blood stream.

Permeation of the lymphatic spaces in the connective tissue, with which the cervix is so richly supplied, is the chief method of spread. Columns of cells creep along these spaces and soon reach the cellular tissue of the parametrium. From there the spread continues forwards to the bladder, backwards through the utero-sacral ligaments to the rectum, and downwards into the vagina. Upward spread into the cavity of the uterus is remarkably rare, the line of the internal os appearing to act as a barrier to the growth.

Spread by the lymphatic vessels with involvement of the lymphatic glands is somewhat capricious. An early case may show extensive glandular involvement, but on the other hand an advanced and inoperable case may show little or none. As with other ulcerating tumors the glandular enlargement may be inflammatory and not malignant. The usual order of involvement is the glands at the base of the broad ligament, the iliac group, the hypogastric group, and the sacral group. The nearest glands may be passed by, however, and secondary growths set up in a more distant group.

Spread by the blood stream is a very late complication, and only occurs in the most advanced cases.

CANCER OF THE BODY

Cancer of the body forms less than 10 per cent of all cases of cancer of the uterus. It occurs later in life than cancer of the cervix, and on that account is usually diagnosed at an earlier date, for as the characteristic hemorrhage occurs after the menopause it is more likely to arouse the alarm of the patient. In sharp distinction to cancer of the cervix it is even more frequent in nulliparous women than in those who have borne children. An association of cancer of the body with fibroids is by no means uncommon, whereas it is distinctly rare in cancer of the cervix.

Gross Appearance.—The tumor arises from the endometrium, usually in the region of the fundus, and the direction of the growth is at first superficial rather than deep, so that a large cauliflower-like mass comes to occupy the cavity of the uterus (Fig. 302). This may be attached to the uterine wall by a more or less narrow base, and in some cases it may become definitely pedunculated, but it is much more usual for it to extend over the endometrium, so that numerous soft sessile masses project from the wall into the cavity. Although spread into the cervical canal might be expected it is of very rare occurrence, and the disease is confined strictly to the body of the uterus. With the progress of the disease the muscular wall becomes infiltrated, but involvement of the parametrium is never early as in cancer of the cervix. The body of the uterus is enlarged, but only to a moderate extent. Ulceration is not common, so that the general symptoms of an infected neoplasm, so characteristic of the later stages of cervical cancer, are rarely seen in this condition.

Microscopic Appearance.—Cancer of the body is an *adenocarcinoma*,

arising from the columnar epithelium covering the surface or lining the glands of the endometrium. The appearance may vary somewhat. Usually the growth is made up of numerous branching tubular glands separated by a scanty stroma (Fig. 303). The lining cells are tall and columnar, and when several layers in depth and irregular in arrangement the malignant character of the condition is quite evident. When a portion of the muscle is present in a scraping the new-formed glands can be seen invading the wall deeply, and the diagnosis is beyond doubt. In some cases, however, the tubules are well formed and lined by but a single layer of columnar cells. If the muscle wall is not present in the scraping the diagnosis may be a matter of considerable difficulty. In such a case particular attention
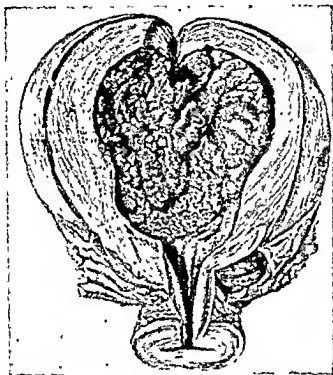
Fig. 302.—Carcinoma of the body of the uterus. A large area is covered by the growth but there is no visible invasion of the muscle.

must be paid to the nuclei of the lining cells. In a normal gland these are all situated at the same level, and are of regular shape and staining properties; the cells are limited by a basement membrane. In carcinoma the nuclei are arranged at different levels, vary in size, some stain dark and others light, and mitotic figures may be seen; there may be no basement membrane.

Very rarely a *squamous-celled carcinoma* may be found, arising, it is supposed, from a patch of leukoplakia, the result of a chronic endometritis.

The tumor may occasionally take the form of an *adeno-acanthoma,* i. e., a combination of glandular and epidermoid carcinoma, some areas showing the one form and adjoining areas the other.

17

Histological grading of biopsy material from carcinoma of the body of the uterus is singularly disappointing and of little prognostic value.

Different blocks from the same case may show widely varying pictures, and biopsy material may differ widely from that obtained by hysterectomy (Cosbie and Henderson).

Spread.—Cancer of the body has not the same powers of infiltration as cancer of the cervix. It is more amenable, therefore, to operative treatment. But although growth is at first centripetal rather than centrifugal, invasion of the muscular wall steadily goes on until, at a somewhat late date, the parametrium is reached. In some cases the growth may pass out along the Fallopian tube and infect the ovary. The lymphatic glands at the side of the vertebral column may be involved late in the disease, and blood spread with metastases in the internal organs is also a terminal manifestation.

Fig. 303.—Adenocarcinoma of body of uterus, invasion of muscularis. × 85.

SARCOMA OF THE UTERUS

Sarcoma of the uterus may occur as a malignant degeneration of a pre-existing fibroid; this is much the most common form, and has already been described on page 475. Or it may occur *de novo* as a distinct rarity. It is the latter form which is discussed here. In contradistinction to carcinoma of the uterus, the condition is much more common in the body than in the cervix.

The tumor may arise: (1) in the uterine wall, (2) in the endometrium.

Sarcoma of the uterine wall may be diffuse or circumscribed. The diffuse form, so rare that it need not be considered here, produces a soft uniform enlargement like that of the pregnant uterus.

The circumscribed sarcoma commences in the uterine wall, but often becomes submucous and pedunculated. These uterine polypi may be removed a number of times before their true nature is recognized, and are apt to be regarded as recurring fibroids. The gross appearance is similar to that of a sarcoma arising in a fibroid, and is such as at once to arouse suspicion. It is soft, even brain-like, homogeneous, yellowish-pink in color, and frequently shows hemorrhages and cyst formation. It will be noted how much the tumor differs from the ordinary fibroid. Microscopically the tumor is made up of round cells or spindle cells.

Sarcoma of the endometrium differs in no important particular from sarcoma of the uterine wall. It may be diffuse or circumscribed, and the appearances are those already described. The line of division between the thickened mucosa and the muscular wall is curiously well maintained.

A very remarkable and interesting form of sarcoma of the endometrium is the *grape-like sarcoma of the cervix* (Fig. 304). This tumor is peculiar in that it may occur at any age, even in infancy. It springs from the cervical canal or the vaginal portion of the cervix, and projects into the vagina as a group of polypoid masses, often likened to a bunch of grapes. The cyst-like appearance of the masses is due to edema of the sarcoma. The cells are round or spindle shaped, but striated muscle fibers have been described, and by some the condition is regarded as a rhabdomyoma.

The *spread* of sarcoma of the uterus is both local and general. The disease tends to spread throughout the uterus and to invade the parametrium, although the latter tendency is not so marked as in carcinoma of the cervix. In the later stages there is blood spread with involvement of the lungs, liver, and other distant organs.

CHORIONEPITHELIOMA

One of the most remarkable tumors in the body is the chorionepithelioma, which usually commences in the uterus, although cases have been described occurring in the Fallopian tube, the ovary, and even in teratomatous tumors of the testicle. The tumor is unique in that it is derived not from the tissues of the patient but from those of another individual, for it arises from the cells covering the chorionic villi.

Fig. 304.—Grape-like sarcoma of cervix. This specimen was removed from a child one year of age.

The condition comes on after pregnancy or even more frequently after an abortion. In about one third of the cases the preceding pregnancy, terminated in the formation of a hydatidiform mole. It is difficult to say exactly how great is the danger of a hydatid mole being followed by chorionepithelioma, but it has been estimated that in about 15 per cent of cases this malignant change may occur. Both chorionepithelioma and hydatidiform mole are frequently associated with a remarkably large, sometimes bilateral, corpus luteum, an organ the function of which appears to be to stimulate the activity of the syncytial covering of the chorionic villi, and thus ensure the firm fixation of the embryo to the uterine wall.

The onset of the growth may be soon after the termination of pregnancy, so soon, indeed, as to suggest that the symptoms may be due to retained products of conception. At other times, however, many months or it may be years may elapse between the appearance of the tumor and the date of the last pregnancy.

Gross Appearance.—The tumor usually commences at the fundus of

the uterus at the placental site. When an early case is examined it is found that the first appearance of the growth is not in the endometrium but in the muscular wall itself. Extension takes place into the cavity of the uterus and to a lesser extent into the muscular wall, so that a soft, hemorrhagic, maroon-colored mass is formed which causes moderate enlargement of the uterus. There is a curious tendency to the formation of secondary growths, sometimes on the lower part of the uterine wall, sometimes even on the wall of the vagina. This is due to a local retrograde bloodstream embolism in the vulvo-vaginal veins caused by occlusion of the large veins in the uterine wall and diversion of the venous flow into tributaries and collaterals, with the formation of bluish nodules in the vagina and vulva.

Microscopic Appearance.—In order to understand the microscopic appearance brief reference may be made to the structure of a normal chori-
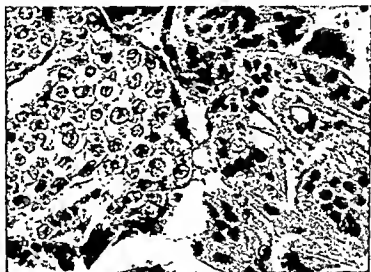
Fig. 305.—Chorionepithelioma. To the left is a mass of clear Langhans' cells. To the right, as well as above and below, are the dark multinucleated syncytial masses. × 400'

onic villus. The villus is covered by the trophoblast, of fetal origin, consisting of two types of epithelial cell, an inner layer of small cubical clear cells with large pale nuclei, the Langhans' cells, and an outer layer of dark undifferentiated protoplasmic masses with dark nuclei, the syncytial layer. Both of these layers are invasive in function, and therefore readily penetrate the walls of blood vessels.

The chorionepithelioma consists of irregular masses of Langhans' cells closely packed together, with here and there the dark multinucleated syncytial elements (Fig. 305). There are no regular stroma nor blood vessels, the tumor cells deriving their nourishment from the blood with which they are so abundantly bathed.

The work of Ewing, Geist, and others has shown that chorionepithelioma does not present a uniform clinical and pathological picture. Some cases run a benign course, others an intensely malignant one. Two main

varieties may be distinguished, between which, however, there are many intermediate grades which add greatly to the complexity of the subject and to the difficulties of diagnosis. The first is the typical chorionepithelioma of Marchand which may be called a choriocarcinoma; the second is the atypical chorionepithelioma of Marchand, which may be called a syncytioma.

The characters of the *choriocarcinoma* are those which have just been described. It is a true malignant tumor, with markedly invasive properties, and a great tendency to set up metastases. Both syncytial and Langhans' cells are always present. Even in this variety abdominal hysterectomy offers fair chances of success.

The *syncytioma* is also a true tumor, but with markedly regressive tendencies, and it does not set up secondary growths, although it may produce abundant hemorrhage from local invasion. It consists of groups and islands of syncytial cells, often giant cell in type, but the bulk of the mass is made up of blood clot and necrotic tissue. No Langhans' cells are present. Its regressive character is evidenced by the spontaneous disappearance of the tumor which sometimes occurs. Even in the more malignant varieties of chorionepithelioma, however, this particular regressive tendency may manifest itself, for not only the primary growth but even the metastases may disappear in the same mysterious manner, a remarkable process which may actually be watched in the case of metastatic nodules on the vaginal wall. This process by which either the primary or secondary tumors may disappear by "killing themselves" is due to extensive hemorrhage and necrosis which entirely destroy the malignant tissue.

Owing to the large amount of gonadotropic hormone produced by the chorionic epithelium, the Aschheim-Zondek test is markedly positive. This test is of value for prognosis as well as diagnosis. It quickly becomes negative after complete removal of the tumor, but if metastasis has occurred it remains positive or again becomes positive after an interval sufficient for the development of the secondary tumors.

THE FALLOPIAN TUBES

It would almost appear as if nature had designed the Fallopian tubes to become the seat of an infective process, and were this the case the attempt has certainly been a successful one, for few organs are more frequently affected by inflammation, both acute and chronic. The tube is open at both ends, so that infection may enter from either end, as well as through the blood stream. The uterine outlet is extremely narrow and may readily become blocked by swelling of the mucosa, so that efficient drainage is impossible. Finally the innumerable folds of the mucosa are admirably adapted to harbor microorganisms for long periods of time.

The tubal epithelium shows similar changes to those of the endometrium in the menstrual cycle. For details of the cytological appearances the illustrations in a paper by Novak and Everett may be consulted.

The most important pathological condition affecting the tubes is inflammation. Tumors are rare and of minor importance.

Salpingitis or inflammation of the tubes may be due to *pyogenic* bacteria or to the tubercle bacillus. These two varieties differ in several

important particulars and will, therefore, be considered separately. By far the most frequent pyogenic cause of salpingitis is the gonococcus, which is responsible for about 75 per cent of all cases. In puerperal sepsis the streptococcus may readily infect the tube.

Some conclusions from a paper by Curtis on the bacteriology of the Fallopian tubes are of interest. He found that in a series of 300 cases of salpingitis 70 per cent were certainly and 10 per cent were probably due to infection with the gonococcus, 15 per cent to other pyogenic organisms, notably various types of streptococci, and 5 per cent to the tubercle bacillus. B. coli was frequently found in tubo-ovarian abscesses of large size, but as a primary cause of salpingitis neither the colon bacillus nor the staphylococcus was of importance. Gonococci were never obtained in culture more than two weeks after the subsidence of the fever. The Fallopian tube, therefore, does not appear to be a focus for chronic gonorrheal infection, and persistently active gonorrhea of the tubes is due either to recurrence of infection from without or to repeated invasion of bacteria from the chronically infected lower genital tract. On the other hand streptococci of various types were isolated many months or even years after the introduction of infection.

GONORRHEAL SALPINGITIS

The gonococcus may reach the tube soon after the initial infection, or a long interval may elapse. The latter cases are probably due to a latent infection in the cervix awakening to fresh activity. The infection, which is
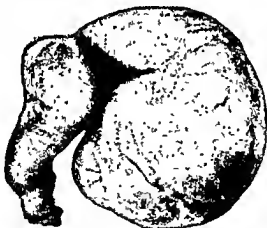
Fig. 306.—Hydrosalpinx. The ostium of the tube is so completely closed that no trace of it can be detected.

practically always bilateral, may be mild, giving rise to a catarrhal salpingitis, or virulent, in which case a purulent salpingitis results. In the catarrhal form there is little structural alteration in the tube, apart from swelling of the mucosa, but with repeated attacks the ends of the tube may become closed and a hydrosalpinx is formed.

Hydrosalpinx.—The ostium of the tube may become closed in two ways: (1) Owing to the chronic inflammation the fimbriae no longer project

freely from the margin of the opening but become drawn into the mouth of the tube, adhere together, and effectively close the opening. (2) The inflamed fimbriae may become adherent to the ovary or other neighboring structures, and again the mouth of the tube becomes sealed. The extremely narrow uterine end, which is less than 1 mm. in diameter, is readily closed by the inflammatory swelling, and the tube is effectively sealed. The serous secretion of the lining cells gradually distends the tube, and a hydrosalpinx is formed. The distension is always more marked at the distal end, and as the peritoneal covering is not so elastic as the rest of the wall, the distended tube becomes curbed into a characteristic retort-like form (Fig. 306). The walls are thin and may be translucent, for the muscular coat has not been affected and thickened by the inflammatory process. The mucous membrane becomes extremely atrophied. The contents are clear, watery, and albuminous.

Fig. 307.—Pyosalpinx (cut surface) showing retort shape and contents coagulated by the fixation.

ʰ **Pyosalpinx.**—If the infection is a more virulent one a suppurative process is set up. The entire wall, both mucosa and muscularis, is invaded with inflammatory cells, at first polymorphonuclears, but later lymphocytes and plasma cells. The latter are particularly characteristic of chronic salpingitis. The tube is filled with pus. If the ends do not become sealed off the result is a *pus-tube*, with thickened walls and purulent contents. If, on the other hand, the ends are closed a *pus-sac* or pyosalpinx is formed (Fig. 307), the walls of which consist of thickened connective tissue with but little muscle, whilst peritoneal adhesions are almost invariable. The pus obtained at operation is usually sterile, for the infecting bacteria have long since died out, but in more recent cases the gonococcus may be recovered. Secondary infection with Bacillus coli is not infrequent, in which case the pus will have the characteristic coli smell.

Tubo-ovarian Abscess.—That the fimbriae when inflamed may become adherent to the surface of the ovary has already been pointed out. In such

an event it is obvious that any infective material in the tube will have ready access to the ovary. Under ordinary conditions the thick tunica albuginea forms an efficient protection to the ovary, but at the time of the rupture of a ripe Graafian follicle the path is open for any organisms to invade the ovary, and the soft hemorrhagic tissue of the corpus luteum forms an excellent culture medium. In this manner an abscess in the ovary is formed, which may gradually extend until it involves practically the entire organ, whilst it communicates with the pus-sac by an opening which is usually quite narrow. Such a condition is called a tubo-ovarian abscess.

Nodular Salpingitis.—Occasionally in gonorrheal salpingitis but more frequently and to a greater degree in the tuberculous form, the isthmus of the tube may be remarkably thickened and present a curiously nodular appearance, so that the condition has been named *salpingitis isthmica nodosa*. The changes in the wall of the tube are somewhat peculiar. In addition to the usual inflammatory infiltration and edema of the muscularis the epithelial elements become pressed between the muscular fibers, where they proliferate and form new glandular spaces. These may at first communicate with the lumen of the tube, but eventually they become completely shut off, so that adenomatous like masses are seen deep down in the muscularis. It will be readily understood that should an ovum wandering down the tube become entrapped in one of these diverticula and then impregnated, a tubal pregnancy will almost certainly result. Although this condition is not uncommon in gonorrheal salpingitis it is more characteristic of the tuberculous form.

TUBERCULOUS SALPINGITIS

Tuberculosis of the Fallopian tube is always secondary to some tuberculous focus elsewhere in the body, frequently in the lung or the bronchial glands. When once infected the tube may act as an important source of

Fig. 308.—Double tuberculous pyosalpinx. The tubes are distended with pus almost gelatinous in consistence.

infection for the peritoneum, so that a tuberculous peritonitis frequently proves intractable until the tuberculous tubes have been removed.

Fig. 309.—Tuberculous salpingitis. Tubercles of various size cover both the tube and the broad ligament. The tube is much thickened.

The infection usually reaches the tubes by the blood stream, occasionally through the ostium from a tuberculous peritoneum, and almost never from the uterus. The condition is practically always bilateral.

Fig. 310.—Subserous cysts of Fallopian tube. × 30.

The ostium usually remains open, in contrast to what occurs in gonorrheal salpingitis. Occasionally it may be closed, so that a tuberculous pyosalpinx develops (Fig. 308). Only rarely does a hydrosalpinx form. The pus-sac contains material which is more inspissated and mushy than

in the gonorrheal variety, and in old cases it may become quite putty-like. In the event of a mixed infection occurring the contents will be fluid and in no way characteristic. Fibrosis of the wall is a marked feature, so that in places the lumen of the tube may be obliterated. Nodular salpingitis of the isthmus is often quite pronounced. The adhesions which are so frequent an accompaniment of tubal inflammation are often extraordinarily dense in the tuberculous variety, so much so indeed as to make removal in some cases impossible.

The *diagnosis* of tuberculous salpingitis when the abdomen has been opened may be easy or very difficult. When the serous coat is studded with miliary tubercles the diagnosis is self-evident (Fig. 309). The small white subserous cysts which are frequently seen on the surface of the tube must not be mistaken for tubercles (Fig. 310). These are probably due to downgrowths of the serous coat, the result of a mild form of inflammation. In other cases no tubercles can be seen, and the final diagnosis may have to depend on microscopic examination of the tube wall.

TUBAL PREGNANCY

Many factors may lead to the arrest of the impregnated ovum in the Fallopian tube, but by far the most important of these is a preexisting chronic salpingitis, a condition in which the folds of mucous membrane become thickened and matted together, deep glandular pockets are formed, the helpful cilia are lost, and everything conduces to entrap the ovum on its downward journey.

The ovum may develop in any part of the tube, but the ampullary site is the commonest. When the ovum develops in the outer part of the tube

Fig. 311.—Tubal pregnancy. The embryo is seen lying in the dilated and thickened tube

the ostium usually becomes closed by the end of the second month, when in the inner part of the tube it remains open (Fig. 311).

A certain amount of decidual reaction always occurs at the site of implantation in the tube, but it does not form a sufficient barrier to prevent the chorionic villi from burrowing deeply into the wall of the tube (Fig. 312). In a considerable number of cases there is a marked decidual reaction in the uterus, and in some cases this decidua is expelled as a triangular cast. The uterus becomes enlarged owing to muscular hypertrophy caused by hormonal stimulation. Uterine scrapings may show decidual cells but no chorionic villi, a finding highly characteristic of tubal pregnancy (Figs. 313 and 314).

Fig. 312.—Tubal pregnancy showing chorionic villi at the placental site in the wall of the tube.

Fig. 313.—Decidual cells in tubal pregnancy.

Fig. 314.—Chorionic villi in normal pregnancy.

There are three chief ways in which a tubal pregnancy may terminate; these are tubal abortion, tubal rupture, and tubal mole. In extremely rare cases the pregnancy may go on to full term within the lumen of the tube.
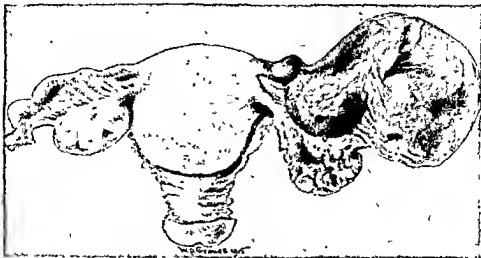
Fig. 315.—Tubal pregnancy. Hematosalpinx. (Graves.)

Tubal abortion is much the commoner method of termination. Owing to the erosive action of the trophoblast the maternal vessels rupture into the gestation sac, converting it into a tubal mole, and the tube itself is distended with blood, a condition of hematosalpinx (Fig. 315). Although hematosalpinx is said in some cases to be due to inflammation of a non-gravid tube, for practical purposes it may be regarded as an indication of tubal pregnancy. The mole consists of a firm mass of blood clot in which chorionic villi may be demonstrated as well as in the tube wall, but it is useless to look for fetal parts. Blood escapes through the ostium and forms a hematocele in the pouch of Douglas which can be palpated on vaginal examination. The mole itself is expelled by the muscular contractions of the tube wall before the ostium has closed at the end of the second month. In the rare cases of pregnancy in the interstitial part of the tube the mole may be expelled into the uterine cavity. Synchronously with the tubal abortion there is a discharge of blood from the uterus. This is not derived from the tube, but from the thickened and congested endometrium. At the same time shreds of decidua may be passed or sometimes a complete decidual cast (Fig. 316).
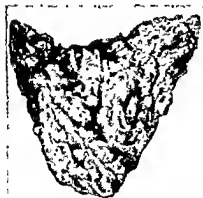
Fig. 316.—Decidual cast.

Tubal rupture occurs in about one fourth of the cases, usually about

the end of the second month, and is due to the chorionic trophoblast destroying the wall of the tube and perforating the serous coat. The sudden rush of blood may constitute one variety of abdominal catastrophe, and the patient dies with symptoms of internal hemorrhage.

In rare cases the fetus may be so slowly extruded through the ostium or a rent in the tubal wall that death does not ensue, connections are formed with the surrounding viscera, and a secondary abdominal pregnancy results which may go on to full term. The fetus then dies, and becomes shrivelled up and converted into a mummified mass, in which lime salts are deposited, a condition of *lithopedion*. In a case in the Winnipeg General Hospital the heart sounds of a seven months' fetus could be distinctly heard, but at operation the fetus was found to lie entirely between the layers of the broad ligament.

Tumors.—There is no common variety of tumor affecting the tube. The most frequent is *primary carcinoma*, which takes the form of an adenocarcinoma. A curious feature is that in 35 per cent of the cases recorded it has been bilateral. The tube is distended by a soft yellowish mass. Primary chorionepithelioma has occasionally been described. Other forms of tumor are too rare to be considered here.

Syphilis.—This is *very rarely seen*. It occurs in the *form of gummata*.

THE OVARY

Inflammation, which is so common and so important in the Fallopian tube, is of minor importance in the ovary. The important lesions are cysts and tumors.

INFLAMMATION

Infection may reach the ovary from the Fallopian tube or through the blood stream. The former is naturally the route of election in gonorrhea and puerperal sepsis, and is much the commoner of the two. The latter method is occasionally seen in infectious fevers, such as typhoid, mumps, etc.

Ovarian Abscess.—After the dehiscence of a Graafian follicle the ovary lies open to infection from the tube, especially as in inflammatory conditions of the tube the fimbriae may be fused to the ovary and thus establish a direct connection between the two organs. The common cause is gonorrhea, but puerperal sepsis may also give rise to this complication. The formation of pus causes gradual enlargement of the ovary, but it is remarkable how few symptoms may develop even when the ovary is little more than a bag of pus. At first the wall of the abscess is formed by the wavy outline of the yellow lutein tissue, but in course of time this becomes invaded by nodular granulations, and the lining membrane is then of a granular faintly yellow appearance, not unlike frog's spawn. The common fusion of the tube to the ovary in inflammation renders communication between an ovarian abscess and a pus-sac very easy, with the production of a tubo-ovarian abscess, a condition which has already been described.

Acute Oöphoritis.—Acute inflammation of the ovary is commonly seen as a part of puerperal sepsis, either from puerperal peritonitis or by infection through the blood stream. In rare cases it may complicate one of the acute infective fevers. Both ovaries are usually involved and are enlarged, soft, very congested, and may contain numerous small abscesses scattered throughout the stroma, the follicles being distended with pus.

CYSTS OF THE OVARY

No organ in the body is so frequently the site of cyst formation as the ovary. These cysts vary greatly in nature. Some appear to be the result of inflammation, retention, or degeneration, whilst others are true tumors or cyst-adenomata. The latter will be considered in connection with ovarian tumors.

Follicular Cysts.—By far the commonest variety of cyst is the follicular cyst, retention cyst, distension cyst, or hydrops follicularis. This is the cyst found in the condition sometimes called sclerocystic disease of the ovary or the small cystic ovary. The cysts are atresic follicles which have failed to rupture owing to the general fibrosis of the chronically inflamed ovary and especially to the thickening of the tunica albuginea. The relation between the cysts and chronic inflammation is, however, by no means proved.

It is difficult to state just at what stage the normal follicle graduates into a follicular cyst. We may say, however, that if it exceeds 1.5 cm. in

Fig. 317.—Lutein cysts of the ovary, with thick wavy lining of yellow lutein tissue.

diameter it should be regarded as exceeding the physiological limits. As a rule the cysts do not attain to any great size, being seldom more than 3 cm. in diameter. They may be single or multiple, and occasionally the ovary may be converted into a tumor riddled with small cysts separated by thin septa.

The cyst wall is composed of fibrous tissue lined by a single layer of epithelium. In the small cysts this may be cylindrical or cubical, but in the larger cysts it becomes flattened. The fluid is clear and of a pale yellow color. Hemorrhage is rarely observed. The ovum cannot be found.

Follicular cysts may occur at any period of life up to the climacteric. They have even been described in the fetal embryo. As far as is known they give rise to no symptoms.

Lutein Cysts.—If maturation precedes the cyst formation the result will be a lutein cyst. Such a cyst is lined by the characteristic wavy yellow lutein tissue derived from the granulosa cells (Fig. 317). The lutein cells are loaded with a lipoid which stains red with Scharlach R and is anisotropic when viewed by polarized light. In some cases the inner lining of

the cyst may be formed of a single layer of cubical or columnar cells; in others this is absent. The contents may be clear and limpid like those of a follicular cyst, but frequently they are tinged with blood, and a frank hemorrhage is a common occurrence. Sometimes they are jelly-like, probably owing to the coagulation of fibrinogen derived from the blood.

The cysts are usually single, but occasionally they may be multiple. Although frequently much larger than the follicular cysts, they seldom exceed the dimensions of a hen's egg. The presence of multiple cysts, however, may lead to the formation of ovarian tumors of considerable size. Such a condition is often bilateral, and is called a compound lutein cyst. Through the thin walls of these cysts can be seen shining the characteristic yellow lining. These large bilateral cysts are nearly always associated with a recent pregnancy, and frequently with hydatidiform mole and chorionepithelioma, conditions to which the excess of lutein tissue may bear some relation. Removal of the mole is often followed by disappearance of the cysts.

Hematoma of the Ovary.—Reference may be made in this place to a blood cyst or hematoma of the ovary. Theoretically this may be due to hemorrhage into any variety of cyst, but actually the only cyst commonly affected thus is the lutein cyst. The cyst is filled with a blood clot of varying size, and the walls present a flattened lutein lining. Occasionally after dehiscence of a ripe follicle bleeding may continue into a true corpus luteum, with the formation of a hematoma. Large quantities of blood are liable, however, to escape into the peritoneal cavity, and there may be alarming symptoms of internal hemorrhage suggestive of a ruptured tubal pregnancy. Such a hematoma may be distinguished from that arising from a lutein cyst by the thick and wavy character of its yellow lining.

Endometrial Cysts of the Ovary.—The subject of "chocolate-colored cysts" of the ovary has already been discussed in connection with the general subject of endometriosis. They are small in size, usually from 2 to 4 cm. in diameter. The lining of the cavity may be smooth and grey, or rough and brown owing to pigmentation from old hemorrhage. They frequently contain menstrual blood, and the surrounding tissue shows the characteristics of endometrial stroma. There may be evidence of previous perforation on the surface, and dense adhesions often develop as the result of the rupture. These adhesions also consist of endometrial tissue. Sampson regards the cysts as endometrial implants, but it appears more probable that they should be regarded as evidence of metaplasia due to hormonal stimulation of a tissue which is related developmentally to the endometrium.

TUMORS OF THE OVARY

Classification of ovarian tumors is peculiarly difficult, because they consist of tissues which are different from those of the normal ovary, whereas in other organs a tumor is, at least in some degree, a duplication of that organ. The tumors may be cystic or solid. The solid tumors may be benign (fibroma, etc.) or malignant (carcinoma and sarcoma). In addition there is a group of tumors associated as a rule with sexual endocrine dysfunction for which there is no very appropriate name, but which may be called the special group.
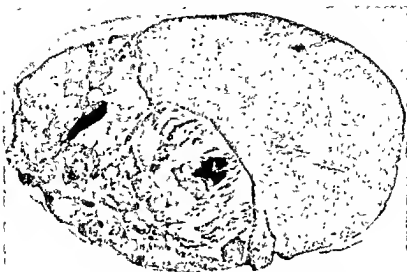
Fig. 318.—Pseudomucinous cyst-adenoma.

Fig 319.—Pseudomucinous cyst-adenoma of the ovary. The spaces were filled with thick slimy material.

The cystic tumors are by far the more common, and are known as cyst-adenomas. Sometimes they are loosely spoken of as ovarian cysts. There are two main forms of cyst-adenoma: the pseudomucinous, and the serous. The latter is sometimes called papillary, but papillary processes may also be found in the pseudomucinous variety.

Pseudomucinous Cyst-adenoma.—This is called cyst-adenoma pseudomucinosum, because the cysts contain a stringy mucoid substance, which, however, is not true mucin, as it does not give the typical reaction with acetic acid, and is therefore known as pseudomucin.

The tumor, which is usually unilateral, may attain enormous dimensions so as to fill the entire abdominal cavity. Nowadays, however, such monstrous growths are rarely seen. The lining epithelium, to whose secretory activity the cysts are due, sends out bud-like projections which are rapidly converted into daughter cysts (Figs. 318 and 319); these in their turn give rise to granddaughter cysts. A few cysts usually enlarge at the expense of the others, and the walls of the smaller cysts are broken down, remaining as ridges and septa which project into the remaining cavities
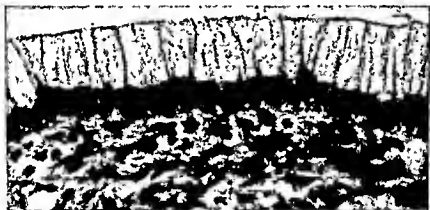
Fig. 320.—Palisade cells with basal nuclei in pseudomucinous cyst-adenoma. × 500.

There is a well-developed pedicle which may rotate axially, because the tumor does not grow between the layers of the broad ligament. Unlike subperitoneal fibroids it may form adhesions to the surrounding viscera.

Microscopic Appearance.—The microscopic picture is very characteristic. The cysts are lined by a single layer of tall, palisade, columnar epithelial cells, curiously clear, distended with mucus so that goblet cells are frequently seen, and with small nuclei at the base of the cells arranged in a regular and uniform row (Fig. 320). Here and there small spurs of epithelium may project into the lumen of the cyst, but they are not a marked feature as in the papillary variety of cyst-adenoma. The cysts are separated by a small amount of connective tissue.

The *contents* of the cysts consist of a stringy, mucinous material, but varying much in consistence *as well as in color*, sometimes clear and transparent, sometimes murky and tinged with blood, sometimes greenish and shimmering due to the presence of cholesterin crystals. This material is called pseudomucin.

Pseudomyxoma peritonei is a condition in which the contents of the

cysts are discharged into the peritoneal cavity, where they form masses of jelly-like material which act as an irritant, causing fibrous tissue proliferation in the peritoneum, so that eventually it may be impossible to remove the masses. At the same time the epithelial cells of the tumor may become detached and implanted on the peritoneal surface continuing there their secretory activity and thus producing fresh masses of jelly-like material. If the ovarian tumor be examined it will usually be found to present a condition of *pseudomyxoma ovarii;* the cysts are filled with the same clear material, and the lining cells have lost their characteristic appearance and are converted into a degenerated amorphous mass. Although the peritoneal condition cannot be regarded as a malignant one, yet the prog-
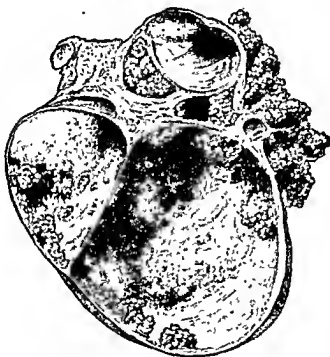
Fig. 321.—Papillary cyst-adenoma of the ovary. The papillomatous masses have appeared on the outer surface as well as on the inner. (After Cullen.)

nosis is not good, for the masses may continue to grow in spite of repeated laparotomies, and the chronic peritonitis may eventually lead to the death of the patient.

Serous Cyst-adenoma.—This form, which constitutes about one-third of the cystic tumors of the ovary, may show different degrees of development. Thus there is the simple serous cyst which is a single cyst with smooth wall, the multiloculated serous cyst without papillary processes, and the multiloculated papillary serous cyst. Although small papillary processes may occasionally be found in the pseudomucinous cysts, it is only in the serous cysts that they attain to any marked degree of development. The cyst-adenoma serosum papillare, as it is called, constitutes about one-third of the cystic tumors of the ovary.

These tumors are frequently bilateral but it must be remembered that the two growths may not be of the same age. They may not possess the well-marked pedicle so characteristic of the multilocular cyst, and often they are found growing between the layers of the broad ligament and are

Fig. 322.—Ciliated epithelium in serous cyst-adenoma. × 240.

therefore difficult to remove. The cyst is usually unilocular but ridge-like projections representing former septa may still persist. The growth is slower than in the pseudomucinous variety, and the tumors never attain to so great a size. The contents are thin, watery, highly albuminous, but contain no pseudomucin. The most important characteristic of the tumor

Fig. 323.—Malignant papillary cyst-adenoma of ovary. × 15.

is the papillary processes with which the wall may be studded. They may be scattered diffusely over the entire wall (Fig. 321), or may be collected here and there into larger nodules. The processes, in common with the rest of the wall, are covered by a single layer of epithelium, which is low columnar and usually ciliated, thus differing from the epithelium of the multilocular cysts (Fig. 322). The processes may be simple in form but

occasionally they are highly branched indicating a marked degree of proliferative activity.

Papillary cyst-adenomas have a very distinct tendency toward malignant degeneration; the more branched the processes, the greater does this tendency become. Malignant change is indicated by the soft character of the papillary processes and the irregular, disordered arrangement of the epithelium (Fig. 323). Even when no malignant anatomical change can be detected, the processes may perforate the wall of the cyst, appear on its outer surface (Fig. 324), become disseminated over the surface of the peritoneum, and give rise to rapid and extensive ascites. The percentage of cases which become malignant varies considerably in the statistics of different authorities. For the most part it is about 20 per cent. Erdmann and Spaulding in a study of papillary cyst-adenomas of the ovary claim that in 66 per cent of their cases there were cancerous or preancerous

Fig. 324.—Malignant papillary cyst-adenoma of ovary in a girl aged 19 years. The papillary processes have ruptured the capsule of the tumor.

changes. These changes are frequently only to be recognized under the microscope. It is therefore necessary to examine for malignancy every warty or papillary intracystic growth and every secondary cyst however small.

The *prognosis* of the papillary cyst-adenomas is variable, and is not necessarily related to the microscopic picture. That picture may appear to be perfectly benign, and yet the clinical course may be a malignant one. On the other hand even when the condition is undoubtedly malignant the rate of progress is often much less rapid than in other malignant growths. Cases presenting numerous peritoneal metastases have been known to live for 9 and even 12 years. Two of our cases made such an apparently complete recovery after the partial removal of an undoubtedly malignant growth that for a long time doubt was cast on the diagnosis. Eventually the disease nearly always ends fatally when dissemination of

the papillomata has occurred, but there are cases on record in which removal of the primary growth has apparently been followed by complete disappearance of the secondary deposits, as shown by a subsequent laparotomy.

The *origin* of the serous cyst-adenoma is the germinal epithelium, for all stages can be traced from simple invagination of this epithelium to the formation of fully developed papillary serous cyst-adenomas. The origin of the pseudomucinous cyst-adenoma is much more doubtful, for the type of epithelium of which it is composed does not occur in the normal ovary. Those who have studied the matter most closely believe that the lesion represents a one-sided development of a teratoma in which the tall, columnar intestinal epithelium has replaced the other elements of the growth, just as the cartilage of a testicular teratoma may proliferate and give a picture of chondroma. In an ovarian teratoma one may find small cysts lined by typical pseudomucinous epithelium. In support of the view that the epithelium is intestinal in nature, Novak points out that in mucocele of the appendix, a lesion which may give rise to pseudomyxoma peritonei, the epithelium is of the same pseudomucinous type.

CARCINOMA

Cancer of the ovary may be primary or secondary. The latter is undoubtedly the commoner, although its secondary nature is frequently overlooked by the clinician.

The terminology of carcinoma of the ovary is apt to be confusing, for the word secondary is used in two senses. The tumor may be strictly primary, commencing as a solid malignant tumor. Or the initial lesion may be a cyst-adenoma which later becomes malignant. This form is called by some gynecologists secondary carcinoma, but the term is undesirable for obvious reasons. It is better to speak of a malignant cyst-adenoma or merely of a carcinoma. True secondary carcinoma may be called metastatic carcinoma to avoid confusion.

Primary Carcinoma.—This *occurs* at the usual cancer period. It is bilateral in about 50 per cent of cases. This does not mean that the growth commences primarily in both ovaries. The second ovary is most probably always infected from the first, the tumors are therefore of very different size.

The *gross appearance* depends on the amount of fibrous stroma. Most of the tumors are highly cellular, and these are soft, friable, at times almost brain-like. If the tumor has developed from a cyst-adenoma, more or less of the original cyst structure may remain, in which the malignant tissue is represented by firm knobby areas. In other cases the original cyst has been almost entirely replaced by tumor, so that the mode of origin may be more than doubtful. Cyst-like spaces without a true epithelial lining are due to degeneration.

The *microscopic appearance* is very variable. We may distinguish three main types. (1) The *papillary* form due to malignant change in a papillary cyst-adenoma (Fig. 325). (2) An *adenocarcinoma* with the formation of irregular glandular spaces lined by several layers of epithelium; in this form large cystic spaces are common. (3) *Carcinoma* ---

plex, consisting of solid masses of carcinoma cells separated by a varying amount of stroma.

Metastatic growths are common owing to the tendency of the carcinoma to break through the tunica albuginea of the ovary. The metastases are scattered over the peritoneum and are largely responsible for the characteristic ascites. Secondary growths may be found in the uterine muscle owing to passage of the cells along the Fallopian tubes. The uterus must therefore always be removed along with both ovaries. In such cases it may be difficult or impossible to determine whether the growth originated in the ovary or the uterus.

The *origin* of ovarian carcinoma is a matter of uncertainty. Many of the tumors arise from the malignant transformation of a cyst-adenoma, usually serous, occasionally pseudomucinous. Such tumors may still re-
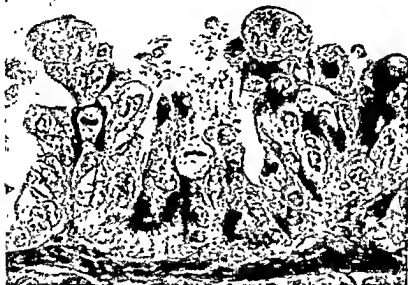
Fig. 325.—Carcinoma of ovary secondary to papillary cyst-adenoma. Note mitotic figures. × 500.

tain their cystic character, or the cysts may be completely replaced by solid tissue. It is believed by some workers that a carcinoma originally solid may become cystic; this seems improbable, and is extremely difficult to prove. In rare cases epidermoid carcinoma may arise from a dermoid cyst. The origin of the primarily solid types is still more obscure. The germinal epithelium, the epithelium of the follicles and Wolffian rests have been suggested. Sampson believes that some cases of adenocarcinoma may arise in areas of ovarian endometriosis.

Secondary Carcinoma.—Postmortem examination shows that this condition occurs much more frequently than the surgeon suspects. Small metastatic deposits go undetected, as they give rise to no symptoms. On the other hand a large ovarian tumor may claim the surgeon's undivided attention, whereas at autopsy it is found to be secondary to a small silent

nodule in the stomach. The growths are almost always bilateral, although one may be considerably larger than the other. The surface is usually smooth or only finely nodular. The primary growth is most commonly found in the stomach or the large bowel. The uterus is another common source of infection.

The *microscopic appearance* is usually a reproduction of the primary tumor. The so-called *Krukenberg tumor* is characterized by the development of droplets of mucin within many of the cells, as a result of which the nucleus is flattened and displaced to one side, whilst the body of the cell becomes clear (Fig. 326). These cells are appropriately called *signet-ring cells,* and the tumor is known as *carcinoma mucocellulare.* As a rule the primary tumor in the stomach or bowel is a mucoid carcinoma, but this is not always the case. Apparently carcinoma cells growing in the substance of the ovary may acquire an ability to produce mucin which they do not possess in the primary lesion. The cells may break down

Fig. 326.—Krukenberg tumor showing signet-ring cells. × 275.

and liberate mucin into the surrounding tissue (where it can be demonstrated by means of a stain for mucin), so that the cellular pattern of the tumor is wiped out. The stroma may be richly cellular, and this,

Fig. 327.—Bilateral Krukenberg tumors of ovaries secondary to cancer of stomach.

when combined with scarcity of epithelial elements, may lead to a mistaken diagnosis of sarcoma of the ovary, an error into which Krukenberg fell. The microscopic appearance tends to vary in different parts of the lesion, so that the cut surface of the Krukenberg tumor is characteristi-

cally variegated, some parts being firm, some soft, and some myxomatous
or cystic.

The *route of spread* probably varies. It is thought by many that
dissemination of cancer cells throughout the peritoneal cavity and implan-
tation on the surface of the ovaries is the common method. This mode of
spread was beautifully illustrated in one of my cases where there was a
small mass in the stomach, numerous tiny metastatic nodules all the way
down the peritoneum, and large carcinomatous masses in both ovaries
(Fig. 327). Against this conception is the fact that the tumors are usually
in the interior rather than on the surface of the ovaries. Retrograde lym-
phatic spread to the lumbar glands and thence to the ovaries is a reason-
able explanation in most cases. In one autopsy I found no tumor on the
serosa of the stomach or the surface of the ovary, but there was marked
involvement of the abdominal lymph nodes, the lymphatics of the ovary
were filled with tumor cells, and there was a large ovarian tumor. The
possibility of occasional spread by the blood stream cannot be denied.

DERMOID CYST

A dermoid cyst is a form of teratoma, the only form commonly found
in the ovary. It constitutes about 10 per cent of all ovarian tumors. In
over 10 per cent of cases it is bilateral, and there may even be multiple
dermoids in one ovary. It may occur at any age period. It is of slow
growth, seldom attains a size larger than a man's fist, and possesses a well
marked pedicle which is liable to undergo torsion. It is an innocent tumor,
but in rare cases one of the epithelial elements which it contains may
undergo malignant change. In a sense it is not a true dermoid cyst, for
such a cyst should be lined by and contain only dermal structures.

The exterior is smooth and glistening, and the yellow color of the con-
tents can often be made out. When removed from the body the wall soon
dries and becomes crackly and the contents, which are fluid at body tem-
perature, become semi-solid so that the tumor develops a doughy con-
sistence.

The interior is filled with a yellow, greasy, buttery material, frequently
containing long wisps of hair, which may be rolled into balls. The hair is
seldom the same color as that on the head of the patient, but with ad-
vancing age it is said by Bland-Sutton to turn white and may eventually
be shed, so that the tumor actually becomes bald. Many other interesting
facts in relation to dermoid cysts of the ovary may be found in Bland-
Sutton's treatise on tumors.

The wall is lined by a cubical epithelium. From one part of the wall
springs a nipple-shaped mass covered with skin called the dermoid process.
This is the essential part of the tumor, as it is from it that the various
solid elements are derived. Of these the commonest are skin, hair, and
bone, but teeth, cartilage, brain, striated muscle, and many other partially
developed structures may occasionally be found (Fig. 328). In one case
which I examined the principal structure was thyroid tissue, so perfectly
formed that it could not be differentiated from a normal thyroid. In
exceptional cases the thyroid tissue either in a dermoid cyst or in a solid
ovarian teratoma may proliferate to such a degree that the tumor consists

almost entirely of this tissue. Such a condition is known as *struma ovarii* (Fig. 329).

Fig. 328.—Dermoid cyst of ovary containing teeth and hair.
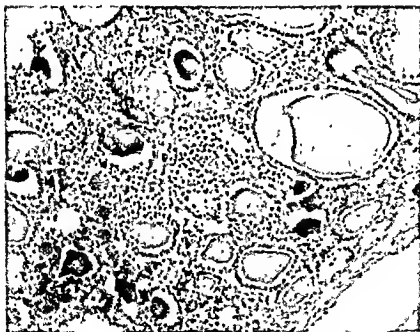
Fig. 329.—Struma ovarii. × 170.

The skin is particularly rich in sebaceous glands (Fig. 330), from the secretion of which the contents of the cyst are derived. The cyst, therefore,

may be looked upon as a secondary formation due to the distension produced by the gradual accumulation of the secretion of these glands.

Both dermoid cysts and solid ovarian teratomata are supposed to arise not from the original ovum, but from one of the blastomeres formed by primary segmentation of the fertilized ovum becoming separated and included in the ovary. If this blastomere is transported elsewhere a teratoma may arise in that part of the body.

Solid Ovarian Teratomata.—These are very rare tumors. They differ from the teratomatous dermoid cyst in being solid, and in possessing no fully formed structures such as skin and bone. They present a large variety of tissues derived from all three embryonic layers, but all in an extremely rudimentary state of development (Fig. 331)

Fig. 330.—Dermoid cyst containing sebaceous glands. × 75

Fig. 331.—Teratoma showing glands, cartilage and fat. × 55.

They form soft, solid masses, which may attain an enormous size and are usually markedly malignant.

Fibroma.—This tumor is uncommon rather than rare. It forms a hard, white or yellowish white mass which is seldom larger than a plum and usually gives rise to no symptoms. More rarely there is a diffuse fibromatosis affecting both ovaries, and these lesions may attain a considerable size and are said to be associated with ascites. A fibroma may present a considerable amount of plain muscle fibers, in which case it is called a fibromyoma.

Sarcoma.—Sarcoma of the ovary used to be a common diagnosis, but it is now known that the great majority of round-celled ovarian tumors are anaplastic carcinomas. Occasionally a true sarcoma, either spindle-celled or round-celled, may occur, but it is a dangerous pathological diagnosis to make.

SPECIAL OVARIAN TUMORS

Of recent years a group of solid ovarian tumors have been described, some uncommon, others very rare, but all characterized by a probable common origin from embryonic remnants (cell rests) and in some in-

stances marked by sex hormone disturbances. Three of these (granulosa-cell tumor, arrhenoblastoma and dysgerminoma) have a common origin from the primitive mesenchyme of the ovary; the fourth (Brenner tumor) is unrelated.

In the developing ovary the granulosa layer of the follicles is formed by differentiation of the mesenchymal *core* of the gonad, not from the surface epithelium as used to be thought. The primitive granulosa cells are therefore connective tissue in type; only later do they develop an epithelial form. It follows that unripe tumors arising from these cells resemble connective tissue, whilst ripe tumors resemble epithelium; sometimes there may be a mixture of types.

The primitive gonad is neither ovary nor testicle, but may develop into either, the direction of the development perhaps depending on the sex of the germ cells which invade the gonad from the primordial gut. Three errors of development are possible: (1) Embryonic rests of undifferentiated mesenchyme may remain and develop years later into a *granulosa-cell tumor*. Such a tumor will produce the female hormone with corresponding structural and functional disturbances. (2) In the primitive gonad, male cells may be formed as a result of faulty development; these may remain as rests, and give rise in later life to an *arrhenoblastoma*, so called because it produces a male hormone (*archen*, male) with corresponding functional disturbance. (3) Cells may be formed which do not develop along either a male or female line, and may be regarded as neuter. Years later these may give rise to tumors which naturally lack the power of producing hormones. In the ovary such a tumor is a *dysgerminoma*;

Fig. 332.—Granulosa-cell tumor.

in the testicle it is known as a *seminoma*. The Brenner *tumor* does not arise from the primitive mesenchyme of the ovary. Its origin is uncertain.

Much of the recent interest which has been aroused by these rare tumors is due tó a series of papers by Robert Meyer. A summary of this work will be found in Novak's monograph.

Granulosa-cell Tumor.—This tumor is also called granulosa-cell carcinoma, but in less than 30 per cent of cases has evidence of malignancy developed. The size varies greatly in diameter—from 1 or 2 cm. to a mass the size of an infant's head. Usually unilateral, the outline is sharply defined (Fig. 332), the outer surface smooth, and the cut surface has a characteristic yellow tinge but is sometimes grey. It may present cysts of varying size, although the smaller tumors as a rule are solid.

The *microscopic appearance* is confusingly varied, and as different parts of the tumor may differ in structure, it is important to cut a number of blocks. Three main types may be distinguished: the follicular, diffuse, and cylindrical. In the *follicular type*, which is perhaps the most common, the granulosa cells are arranged in little clusters or rosettes around a central lumen. To be distinguished from this lumen are the so-called

Call-Exner bodies, which are spaces in larger masses of granulosa cells produced by liquefaction (Fig. 333A). These spaces may contain bodies resembling and formerly mistaken for ova, but in reality secretion or degeneration products. In the *diffuse type* the granulosa cells are arranged diffusely rather than in rosettes. In the *cylindroid* or cylindromatous form masses of epithelial cells are separated by invasion and overgrowth of connective tissue elements so that the appearance is one of anastomosing cylinders (Fig. 333B). Luteinization may occur, *i. e.*, an accumulation of lipoid in the tumor cells. This is readily demonstrated by fat stains such as Scharlach R. The more marked is this process, the more striking is the yellow color of the tumor. When the process is widespread the tumor is spoken of as a luteoma.

The *malignancy* is variable. Most cases pursue a benign course, the tumor often being found incidentally. In other cases there may be perit-
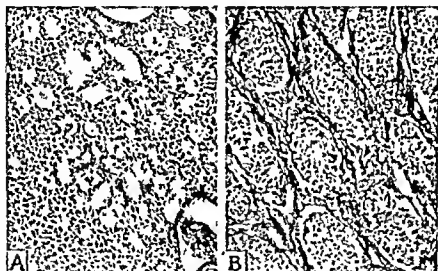
Fig. 333.—Granulosa-cell tumor. A, Diffuse type. × 150. B, Cylindroid type. × 120

oneal recurrence a few months after removal of the tumor. The microscopic picture is of no value in determining the degree of malignancy.

Certain tumors of this series present a connective tissue appearance and are known as *theca-cell tumors*. There is difference of opinion as to whether these lesions should be regarded as a separate entity or as a variant of the granulosa-cell tumor. The latter view seems preferable. The tumor is hard and fibrous looking. As luteinization is common, the yellow color may be marked. Because of the high lipoid content the tumor is also known as *xanthofibroma thecacellulare* and *luteoma*. *Microscopically*, interlacing bands of spindle or epithelioid cells are separated by strands of connective tissue containing *hyaline plaques*. Fat stains show the lipoid to be both intracellular and extracellular; it is doubly refractive, probably cholesterol or cholesterol ester. The arrangement of reticulum as shown by silver stains is distinctive. In the theca-cell tumor the fine threads of reticulum are in relation to individual cells, whereas in the granulosa-cell tumor the reticulum surrounds groups of cells.

The *genesis* of these tumors is usually considered to be granulosa-cell rests which have not been used in the process of follicle formation. When one considers the intimate relationship which exists between the granulosa-cell and theca-cell tumors, it seems more probable that their origin may be traced to primitive mesenchyme which antedates the differentiation of granulosa and theca cells. It may be noted, however, that some workers (Geist, Butterworth) have succeeded in producing granulosa-cell tumors by irradiating mice with X-rays. Such tumors are apparently derived from normal follicles following degeneration of the ova, not from embryonic rests of granulosa cells.

The *clinical effects* of what has been called the feminizing tumor depend on the period of life at which the tumor develops. The granulosa cells produce estrogenic hormone, so that there will be abnormal menstrual bleeding before puberty or after the menopause, but during the reproductive years the only effect is likely to be increase in the flow. In the child there will be precocious puberty, *i. e.*, early menstruation, development of the breasts and external genitalia, and hypertrophy of the uterus. In the adult endometrial hyperplasia may be a marked feature. Carcinoma of the endometrium has developed in a number of cases, surely a point of great interest in connection with the relation of hormones to carcinogenesis. Removal of the tumor in the prepubertal and postmenopausal cases is followed by disappearance of the abnormal clinical features.

Fig. 334.—Arrhenoblastoma. × 240.

Arrhenoblastoma.—This masculinizing tumor is the rarest member of the special ovarian tumors. It arises from the cells of the primitive ovarian mesenchyme which have a male tendency, and it is often found in the region of the rete ovarii, which is the homologue of the male testis. The *gross* appearance is similar to that of the granulosa-cell tumor. The *microscopic* picture varies even more widely than that of the latter tumor. In some cases, but these are the exception, there is perfect reproduction of the seminiferous tubules of the testis, a condition described long ago by Ludwig Pick as testicular adenoma of the ovary (Fig. 334). More usual is a very imperfect attempt at tubule formation, the cells being arranged for the most part in irregular columns. Interstitial cells with the usual lipoid content may or may not be present. At the far end of the scale the cells are completely undifferentiated, giving a picture of sarcoma. A correct diagnosis may be possible through finding attempted tubule formation in other blocks, but in many cases the pathologist is dependent on the characteristic clinical history. In spite of the sarcomatous appearance the tumor is either benign or of low malignancy.

The *clinical effects* are at first defeminizing, later masculinizing. Amenorrhea and extreme atrophy of the breasts are the early signs. These are followed later by hirsutism with masculine distribution of hair, roughening and deepening of the voice, and hypertrophy of the clitoris. The picture is similar to that of tumor of the adrenal cortex, a structure with which the ovary is closely related developmentally.

Dysgerminoma.—This tumor arises from indifferent cells of the mesenchyme in the gonad which fail to develop in either a male or female direction. It may occur in the ovary or testis. In the ovary it is nearly always benign, but in the testis it is always malignant (seminoma). In the ovary it is often bilateral, may grow to a considerable size, and shows a characteristic yellow staining of the cut surface due to lipoid degeneration. It is rubbery in consistence, and areas of necrosis and hemorrhage ore common but without cyst formation.
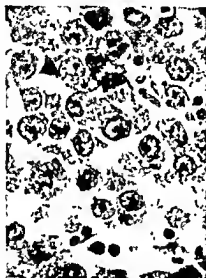
Fig. 335.—Dysgerminoma. × 500.

Fig. 336.—Brenner tumor showing epithelial nest and fibrous tissue. × 80.

Microscopically the tumor is simple in structure, and does not show the marked variation characteristic of the granulosa-cell tumor and arrhenoblastoma. The cells are large and round with vesicular nuclei, similar to those of seminoma of the testis, and in the past the tumor has been called large-cell carcinoma (Fig. 335). The cells shrink to a marked degree when embedded in paraffin, and are best seen in frozen or celloidin sections. The cells are grouped in solid alveoli or in columns, separated by septa of fibrous tissue in which there may be large numbers of lymphocytes. Areas of degeneration and hemorrhages are common.

Although the tumor resembles so closely the seminoma of the testis in microscopic appearance (by some it is called seminoma ovarii), the majority of cases remain benign. The tumor looks malignant but is benign. A small number, however, show malignant characters, invading the capsule and setting up regional and distant metastases.

The *clinical effects* are in striking contrast to those of granulosa-cell tumors and arrhenoblastoma, as might be expected from the fact that the tumor arises from indifferent sex cells. It usually arises in children and adolescents, but may occur in adults. As a rule the patient is normal sexually, but in a number of cases there has been pseudohermaphroditism, sexual hypoplasia or infantilism. This disturbance of development does not appear to be dependent on the presence of the tumor, because after surgical removal there has been no change in the clinical condition.

Brenner Tumor.—The lesion described by Brenner in 1907 but clarified by Robert Meyer in 1932 differs sharply from the group of three "special" ovarian tumors already discussed. The *gross appearance*, particularly when the tumor is small, is that of a fibroma, and in the past it has frequently been mistaken for that condition. When large, for reasons which soon will be apparent, it may take the form of pseudomucinous cyst-adenoma with nodular masses of tumor persisting in the wall. There are wide variations in size; it may be minute or it may be enormous.

The *microscopic picture* has none of the extreme variability so characteristic of granulosa-cell tumor and arrhenoblastoma. There are two essential elements: (1) nests of epithelial cells, and (2) fibromatous connective tissue separating these nests (Fig. 336). The epithelial cells are for the most part strikingly uniform in type, and recall the appearance of a carcinoid tumor of the appendix or bowel. There are no mitoses, nor any suggestion of malignancy. Cystic degeneration in the center of the nests is common, giving rise to an appearance which may be mistaken for follicles. One striking variation from the usual picture may occur, the cells becoming columnar and clear, secreting mucus, and lining spaces, a picture similar to that of a pseudomucinous cyst-adenoma. When this condition is widespread, the gross appearance may be identical with the ordinary cyst-adenoma, and the essential character of the original tumor may be overlooked. The connective tissue elements vary, but may be so abundant that the lesion is mistaken for a fibroma.

The *origin* of the tumor is still a matter of dispute. The commonly accepted view is that of Meyer, who believes that the starting point is the so-called Walthard inclusions. These are minute circumscribed nests of cells which are found in the newborn and young child, not only in the ovary, but also in the tubes and uterine ligaments. Occasionally these take the form of *gland-like spaces lined by columnar epithelium which may secrete mucus.* Other suggestions are a dislocation of cells from the primitive uro-genital connection, and a one-sided development of a teratoma, the latter based on the frequent association with pseudomucinous cyst-adenoma.

The tumor is rare, but many cases must be overlooked. It is of slow growth, and the majority are detected over the age of fifty. There is no endocrine disturbance.

Hypernephroid Tumors.—One of the rarest of ovarian tumors is yellow in color and is composed of clear cells like those of a hypernephroma. Such tumors are therefore called hypernephroid, and are supposed to arise from mesonephric structures within the ovary (Saphir and Lackner).

PAROVARIAN CYSTS

The parovarium or organ of Rosenmüller is situated in the mesosalpinx between the ovary and the Fallopian tube, and can be seen when the mesosalpinx is stretched and held up to the light. It consists of a horizontal tube, the duct of Gartner, which corresponds to the vas deferens in the male, and a series of vertical tubes, homologous with the vasa efferentia and epididymis. These latter are divided into two groups, the outer of which is named Kobelt's tubes.

Cysts arising from the parovarium are of two varieties. The common form, known as a *cyst of the hydatid of Morgagni*, is a small cyst no larger than a pea, filled with clear serous fluid, and attached by a long slender stalk to one of the fimbriae of the tube.

Fig. 337.—Parovarian cyst with small papillary processes.

The ordinary parovarian cyst arises between the layers of the broad ligament. It never appears before the age of puberty, and may enlarge slowly over a period of years until it attains an enormous size. In other cases, however, it may remain quite small.

The wall of the smaller cysts is thin and transparent, but as the cyst grows larger it may become very thick and tough. The Fallopian tube is stretched over the wall of the cyst and may be greatly elongated. The ovary is attached to the side of the cyst, but in the case of large cysts it may be extremely flattened, incorporated in the cyst wall and difficult to recognize. It may be difficult to differentiate these cysts from a papillary serous cyst-adenoma of the ovary which usually occupies the broad ligament. A parovarian cyst, however, seldom presents papillary processes, and when they are present they are usually in the form of small warts on the surface (Fig. 337).

The wall is composed of fibrous and muscular tissue, and is lined by a

low columnar ciliated epithelium. It is usually quite smooth. The contents are clear and watery, with a low specific gravity, and a trace of albumin. In large cysts, however, the fluid may be turbid. The condition is essentially innocent.

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CHAPTER XXIV

THE BREAST

Structure.—The breast is a solid glandular organ developed from either the sweat or the sebaceous glands of the epidermis. It is divided into from 12 to 20 lobes of pyramidal shape, each of which may be regarded as a gland in itself. Each is provided with a milk duct opening at the nipple. Smaller ducts branch laterally from the main duct and end in bulbous expansions or alveoli, which at first are solid, and only contain a definite lumen during and after lactation. Lobules consisting of clusters of alveoli are thus formed within the main lobes. The number of side ducts and end bulbs increase at puberty, and to a much greater extent during lactation.

Fig. 338.—Normal breast showing three gland fields. × 50.

The cells of the large ducts are columnar, of the small ducts and the acini cuboidal.

The glandular elements are separated by fibrous tissue and fat. The ducts are surrounded by a loose cellular connective tissue called the periductal or intralobular tissue (Fig. 338). As the terminations of the ducts are approached it surrounds these both individually and collectively, thus grouping them into definite lobules. The ducts are surrounded by a thin layer of elastic tissue, which Cheatle terms the "elastica." This layer is not prolonged over the acinar wall, but when involution occurs this layer surrounds the acini also. The intervening stroma consists of dense interlobular connective tissue containing a varying amount of fat.

It must be borne in mind that the histological appearance of the breast varies greatly at different ages. In the young virgin the glandular tissue is scanty and the alveoli have not opened out to form a lumen. During lactation there is such an enormous multiplication of ducts and acini that the fibrous stroma largely disappears, and the entire picture is changed. During later life involution changes occur which will be described presently, and the ducts and acini usually present a double layer of lining cells.

The epithelium lining the commencement of the duct is stratified as far as the ampulla, where it gives place to tall columnar epithelium. When the small ducts are reached the epithelium becomes cuboidal, and the terminal acini are lined with the same variety. Although at first sight it appears as if the ducts were lined by one layer of epithelial cells, there is in reality a second flattened layer outside, which may be described as a reserve layer for reproducing the lining cells, much as the basal layer of the epidermis replaces the cells lying superficial to it. MacCarty has pointed out the importance of this reserve layer. Its cells proliferate and enlarge in pathological conditions, so that it is common to find the ducts and acini lined by a definite double layer of cells (Fig. 339). A single layer can seldom be found in a fibroadenoma, in cystic mastitis the cells are frequently several layers in depth, and in carcinoma they have begun to invade the connective tissue stroma.

Fig. 339.—Reserve layer of cells (dark) in duct. × 250.

The breast has an abundant lymphatic supply. The normal drainage is through the axillary glands of the same side. Many vessels open into the large pectoral plexus, which lies in the pectoral fascia between the posterior surface of the breast and the pectoralis muscle. This plexus is simply a part of the deep fascial lymphatic plexus which pervades the entire body. When the pectoral plexus is invaded by carcinoma cells, therefore, there is no limit to the extent to which they may spread by the process of permeation. One lymphatic trunk passes directly through the pectoralis major and empties into the subclavicular glands without passing by way of the axillary glands. For this reason the subclavicular glands may be enlarged in carcinoma before those in the axilla.

Male Breast.—The male breast is similar in development to that of the female, but remains rudimentary throughout life. The fundamental difference in structure between the male and the female breast is that in the former there are no acini but only a series of ducts of fair size. It is liable to the same disease conditions, but with much less frequency owing to its rudimentary state. At puberty there may be temporary congestion and inflammation. In the study of an extensive series of cases Neal found that the most frequent lesions of the male breast were nonneoplastic processes, the next commonest were benign tumors, whilst carcinoma occupied the third place. He found that carcinoma was 80 times commoner in the female breast than in the male.

Functional Changes.—There is no organ with so confused a pathology or so bewildering a nomenclature as the breast; there is no organ the pathology of which as a student the writer found it so difficult to master. The difficulties and roughness of the way will be smoothed, we feel, if the functional variations of the breast together with their corresponding morphological changes be ever kept in mind.

Before the age of puberty the female breast resembles the male in that it possesses ducts but no acini. At puberty the female breast undergoes a great structural change; the ducts commence to branch, and the termina-tions of the smallest branches expand into acini. Many of these acini are so crowded with cells as to appear quite solid and of course functionless, a condition recalling the structure of the fetal thyroid.
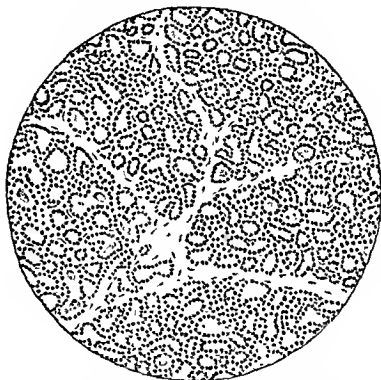
Fig. 340.—Lactating breast, showing the extreme epithelial hyperplasia.

During pregnancy, and still more during lactation, the morphological change is remarkable. The gland becomes the seat of an extreme epithelial hyperplasia, which recalls the hyperplastic thyroid of Graves' disease. The acini are enlarged, large numbers of new acini are formed, the epithe-lium changes from the cuboidal to the tall columnar form, and the lumen of the acini may be crowded with fern-like epithelial projections very much like those of thyroid hyperplasia. It is a picture of unbounded epithelial activity, although differing from that of carcinoma in that the activity is restrained and orderly (Fig. 340).

Although we have not the same definite knowledge of hyperplasia in the breast as in the thyroid, yet there can be no doubt that other stimuli than puberty, pregnancy, and lactation can play upon the breast. The literature contains many examples of the breast showing signs of activity

and even lactation in quite young girls. The relation between the condition of the pelvic organs and activity of the breast is undoubted. When both ovaries are removed before puberty the breast fails to develop. Ovulation, or it may be formation of the corpus luteum, exerts a potent influence on the breast. In many women there is tenderness and swelling of the breast at each menstrual period, and in some cases actual lactation. There is a marked histological difference between the breast during menstruation and the same organ in the intermenstrual period. Rosenberg has shown that coincident with ovulation and the formation of the corpus luteum there is a rapid formation of new lobules of acinar tissue from the epithelium of the small ducts. When impregnation does not occur, these new lobules disappear. When ovulation finally ceases the breast passes into a condition of involution.

For after hyperplasia comes *involution.* As with the thyroid, when the stimulus is withdrawn, activity ceases and the morphological picture changes. Involution is most marked after lactation and at the menopause, the latter being known as senile involution. It also occurs after abortion or pregnancy without lactation. Indeed whenever physiological hyperplasia occurs it will be followed sooner or later by involution.

An *involuting breast* is one which varies greatly in appearance in its different parts, for neither evolution nor involution appear to affect the organ in a uniform fashion. The picture is a mixture of atrophy and hyperplasia, and exactly the same mixed picture is seen in a hyperplastic goiter which is passing into the colloid state. Speaking generally there is an atrophy of the parenchyma with an increase in the fibrous tissue. The columnar cells become cuboidal or flattened. The acini return to their former size and after the menopause disappear altogether. The periductal fibrous tissue may be markedly thickened in the senile breast, and the distinction between interlobular and intralobular connective tissue is lost, so that the outline of the lobules disappears. The elastica, as Cheatle has pointed out, is continued over the cul-de-sac of the acini as well as the ducts. Dilatation of the ducts and of some of the acini is common, with the resulting formation of small cysts. It appears probable that this dilatation is not due, as is commonly taught, to obstruction of the ducts from fibrosis, but is rather an initial increase in size at the time when the acinus was enlarging during hyperplasia. Having failed to return to the normal size, and being emptied of its hyperplastic epithelium, it appears as a cyst. Cyst formation, therefore, may be looked on as evidence of hyperplasia followed by involution rather than retention due to obstruction. Round-celled infiltration around the ducts is seen here and there. For this we can give no satisfactory explanation. It has been suggested that retained secretions may act as an irritant and so set up a mild degree of inflammation.

In addition to these changes, which in general are atrophic, there may be signs of hyperplasia. The cells lining the acini and ducts may be two or more layers in depth, or they may fill the lumen. In some cases the evidence of hyperplasia is even more marked. These appearances are usually taken as indicative of the involution process, but it appears more probable that they represent a *previous* hyperplasia which may not have completely passed off.

So far we have been considering the process of normal involution. There is, however, a process of *abnormal involution*, or perhaps we should rather say an abnormal hyperplasia-involution process. It may be abnormal in that it occurs at an unusual time—before the menopause or apart from lactation—or it may be abnormal in degree and quality. Still more important, it is probably abnormal in regard to the stimulus which calls it forth. Again the changes are atrophic and hypertrophic. It is the hypertrophic change which is much the more important. The acini proliferate, increase in size, and there is a multiplication of the lining epithelial cells. Cyst formation is common, and papillary masses of epithelium often project into the cysts, giving rise to a tumor-like condition. It may be said that the chief microscopic lesion is epithelial hyperplasia, the chief macroscopic lesion cyst formation.

From this general discussion it will be gathered that the breast, like the thyroid, is an organ liable to fluctuation in functional activity and to corresponding morphological changes; that hyperplasia may completely alter the normal appearance of the gland; that hyperplasia may affect one part of the breast and not another; that when involution follows hyperplasia the picture will be still further complicated; that the breast—again like the thyroid—does not return after hyperplasia and involution to a morphological condition which is perfectly normal; that hyperplasia bears a certain resemblance to tumor formation and may easily be mistaken for it; and that cyst formation (corresponding to the dilated acini of colloid goitre) is to be expected as a result of the hyperplasia-involution process. A good discussion of the variability of normal breast structure will be found in a paper by Dawson.

The greatest difficulty in studying breast pathology is the nomenclature. A review of the literature on the breast leaves one in a state of absolute bewilderment. Deaver and McFarland in their exhaustive treatise give 23 names for the condition commonly known as chronic cystic mastitis. A condition such as intracystic papilloma (to give it one of its dozen names) is considered by one author under the heading of neoplasms, by another under that of chronic mastitis. The same used to be true of goitre; every slight variation, often merely dependent on a degeneration, was given a separate name. In both of these cases we are dealing with but one condition, subject it is true to as many variations as a Bach fugue, but with one guiding theme running through them all. Such a conception should make a study of breast pathology a little less confusing.

The common affections of the breast are acute inflammation, chronic mastitis, and tumors. Syphilis is of rare occurrence, and still more rare is tuberculosis.

ACUTE MASTITIS AND MAMMARY ABSCESS

Inflammation of the breast is confined to three periods in the development of the organ: immediately after birth, at puberty, and during lactation. If we exclude conditions of mere congestion which may be almost physiological, and confine the term mastitis to inflammation produced by bacterial invasion, we find that in about 95 per cent of the cases it occurs during the first few weeks of lactation.

The infecting organism is usually the staphylococcus aureus, less com-

monly the streptococcus. The **staphylococcus** is more likely to produce a
localized, the **streptococcus** a diffuse inflammation. The organism may
enter the breast either through the milk ducts or through cracks in the
nipple and thence by way of the lymphatics. The latter is probably the
common mode of entry.

The inflammation starts in the interlobular connective tissue, which
becomes acutely congested and infiltrated with inflammatory cells, the
glandular elements merely showing secondary degeneration. It may in-
volve: (1) the subcutaneous tissue in front of the breast, (2) the breast
itself, (3) the tissue behind the breast; it may thus be subcutaneous, intra-

Parenchymatous
inflammation

Submammary
abscess

Areolar abscess

Phlegmonous inflammation
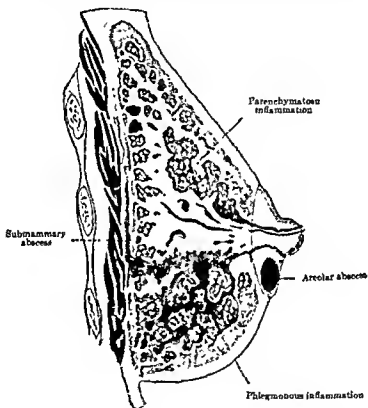
Fig. 341.—Diagram of breast infections. (DeLee.)

mammary, or retro-mammary (Fig. 341). If pus is formed it will reach
the surface with an ease depending upon its depth from the surface. In the
retro-mammary form, due usually to extension of infection from the
breast into the retro-mammary space, but occasionally secondary to dis-
ease of the ribs, the already inflamed breast is pushed bodily forward, as
can be seen by comparison with the gland on the other side.

The condition may end in resolution, but frequently goes on to suppu-
ration with the formation of an abscess. The gland is at first congested,
hot, painful, and hard, but becomes softer as suppuration develops. Only
one segment of the breast may be involved, or the infection may spread

into adjoining lobes, so that a series of abscesses may be formed. These may remain distinct, demanding separate incisions for successful evacuation, or there may be a series of intercommunicating cavities with extensive destruction of breast tissue.

The abscess may discharge on the surface, or, more rarely, into the pleural cavity. Healing with fibrosis occurs in one or two weeks in the superficial variety, but in the deeper forms discharging sinuses may persist for several months. Occasionally the abscess may become encapsulated, the pus absorbed, and all that remains is a mass of fatty and calcareous material. Although painful and disabling, the condition is rarely fatal.

The only condition with which acute mastitis may be confused is acute carcinoma. In the latter condition, which usually develops during lactation, there is rapid enlargement of the breast, the skin is red and inflamed, and there is a considerable degree of fever. The absence of softening, the fixation of the breast, the involvement of the skin, and the marked enlargement of the axillary glands serve to differentiate the two conditions.

Plasma Cell Mastitis.—This rare condition is readily mistaken for carcinoma, because it presents many of the clinical features of cancer. The chief distinguishing features are rapid onset, marked tenderness, and a puriform discharge from the nipple. The condition is a true inflammation, but probably of chemical (retained secretion) rather than bacterial origin. The gross specimen consists of a mass presenting radiating dense fibrous tissue strands and dilated ducts containing creamy puriform material. The microscopic picture is one of subacute inflammation with plasma cells predominating. Giant cells may be numerous. Good illustrations of the lesion will be found in Cheatle and Cutler's monograph on the breast.

LOBULAR HYPERPLASIA—CHRONIC MASTITIS

We now approach a subject which is the root and center of all the difficulties in breast pathology. The first problem which we encounter is to decide by which name the condition should be known. Its names are indeed legion. Amongst the better known are chronic mastitis, chronic cystic mastitis, chronic interstitial mastitis; diffuse fibro-adenoma, cyst-adenoma papilliferum; involution cysts, abnormal involution; cystic disease of the breast, Schimmelbusch's disease. This abbreviated list is given, not with the object of burdening the memory, but that the reader may have some guide when he delves into the literature on the breast.

It is not that the name itself is of such importance, but almost all of these names commit one to a definite theory. The first group suggests that the condition is inflammatory in nature, the second that it is neoplastic, and the third that it is a perversion of involution. The only real evidence in support of the inflammatory hypothesis is the presence of lymphocytic infiltration, and that is always found in involution following lactation and often in senile involution. Nor can we admit that the condition is a neoplasm. There is no tumor—that is a fact from which we cannot get away. It is true that the epithelial hyperplasia may at times suggest a neoplastic process, but the same may be said of the epithelial hyperplasia in goitre.

The best name is that suggested by R. P. Smith, namely lobular hyper-

plasia of the breast, with its subdivisions of localized or generalized, and cystic or non-cystic. Smith's paper consists of only three paragraphs, the last of which may be quoted in full. "Such a classification embraces the majority of the older names. For example, generalized non-cystic lobular hyperplasia corresponds to mazoplasia (Cheatle), the mastopathia of Whitehouse, and the painful nodular breasts of young women, so well known clinically; localized cystic lobular hyperplasia to the solitary blue-domed cyst of Bloodgood; generalized cystic lobular hyperplasia to cystic hyperplasia, involution cysts, abnormal involution cystic disease, and Schimmelbusch's disease, where multiple cysts are scattered throughout the breasts. As the sole cause for regarding the condition inflammatory is the presence of collections of lymphocytes, which are a normal feature in every pregnancy and lactation, and to a lesser degree at every menstrual period, the terms chronic mastitis, chronic cystic mastitis and chronic interstitial mastitis can be dismissed as archaic and should be discarded." Unfortunately it is not easy to cast overboard a term which has become part of the everyday speech of pathologists and surgeons, and it will be some time, even in this book, before chronic mastitis is finally displaced.

Nature of the Disease.—From what has just been said regarding nomenclature it will be gathered that there is no agreement as to the true nature of the condition. By some it is regarded as inflammatory, by some neoplastic, and by still others as a perversion of involution. In a Hunterian Lecture on chronic mastitis Keynes comes to the conclusion that it is not bacterial, toxemic, or traumatic in origin, nor is it related to involution changes in the breast, but that the cause is probably to be found in chemical irritation due to stagnating secretions and epithelial débris. He further points out that the funnel-shaped mouth of a lactiferous duct is lined with an epithelium which normally keratinizes on the surface, and that these cornified layers tend to accumulate so as to form an epithelial plug for the duct in the non-lactating breast. These plugs are well seen in longitudinal sections of the nipple, and should the breast awaken into activity the accumulation of secretion in the plugged ducts may give rise to the condition of chronic mastitis.

What we feel to be a more reasonable explanation and one which brings the condition into line with similar conditions in the thyroid and the prostate is arrived at by comparing the account of the physiological changes which the breast undergoes throughout life with that of the lesions in chronic mastitis. As has just been pointed out, the breast is being continually played on by a variety of stimuli which tend to induce hyperplastic changes followed later by involution. We shall find that the changes characteristic of hyperplasia and of involution may all be duplicated in chronic mastitis (lobular hyperplasia): there is evidence of epithelial activity and proliferation in the form of epithelial buds, later atrophy of the epithelium, cyst formation, fibrosis and round cell infiltration—in short, evidence of hyperplasia which may or may not be associated with involution.

Clinical Features.—The patient comes complaining either of pain or a lump in the breast. The pain, although usually slight, may be severe, is often worse at the menstrual period, and frequently neuralgic in nature. The breast is tender, especially at certain points. One or both breasts may

be involved, and there may be more than one lump in one breast. This multiplicity is always strong evidence against cancer. A granular induration is felt when the breast is palpated between the fingers and thumb, much less distinctly when the flat of the hand is used. In this respect it differs from both innocent and malignant tumors. In thin persons the breast substance has a characteristic ropy feeling. Cysts when present feel hard rather than fluctuating, and give the induration a more coarsely granular character. The induration is frequently confined to one of the sector-like lobes of the breast, whereas in cancer no such restriction is observed. The axillary glands are often enlarged and tender. As in carcinoma they may not be palpable, the condition of the glands should not be used as a means of diagnosis. The cause of the glandular enlargement in lobular hyperplasia is unknown. Although the disease is commonest at the time of the menopause, it may occur before the thirtieth year. Bloodgood states that it is more frequent in the breast which has never lactated, whether there has been pregnancy or not.

Fig. 342.—Lobular hyperplasia, diffuse, cystic. It is not often that the lesion shows so many large cysts.

Gross Appearance.—The lesions found in lobular hyperplasia are so varied that it is difficult to give a comprehensive description of the gross appearance. In a general way it may be said that when incised the indurated area is tough and indiarubbery in consistence, yellowish-white in color, not encapsulated, and not definitely circumscribed. It has not the stony hardness of a scirrhous carcinoma, nor does it present the familiar yellow streaks and specks so characteristic of that condition. The cut surface presents an area rather than a lump, an area whose limits are poorly defined. Pink and grey dots of new-formed glandular tissue may be slightly raised above the surrounding surface. Cysts of varying size and number are usually present, although sometimes so small as to require most careful inspection. In some cases the whole area may be converted into a series of cysts; this is the classical cystic disease of the breast, to which the name Schimmelbusch's disease was originally applied (Fig. 342). Sometimes the ducts of the affected area are dilated with putty-like material which can be expressed as casts resembling small worms. The cells lining these ducts are vacuolated and tend to break down, their cholesterol-rich content filling the lumen.

Bloodgood gives an excellent description of the various forms which the disease may take, but the different varieties are considered almost as separate entities, and no underlying fundamental principle can be traced throughout the series. The paper is of particular value in that the clinical history of the patients has been followed, in some cases for as long as 29 years.

In the 350 cases Bloodgood found 210 with large cysts, either single or multiple, and 140 without large cysts.

By far the commonest type of large cyst is what Bloodgood calls the blue-domed cyst. The blue dome of the cyst is usually seen after dividing the subcutaneous fat, but sometimes a zone of breast tissue has to be divided also. When the cyst wall is nicked the blue color disappears. The contents of the cyst are clear or cloudy, never hemorrhagic. Hemorrhage into a cyst indicates carcinoma. The wall is smooth; there are no papillomata. There were 174 examples of single large cyst in Bloodgood's series.

Of multiple large cysts in one or both breasts there were 28 cases. These cysts also are of the blue-domed variety. This is the classical cystic disease of the breast. The gland is riddled with large cysts of the same character as just described.

In 8 cases the cyst resembled a galactocele, although none of the cases had any relation to lactation. This cyst is white-domed, contains a milky fluid, and the contents coagulate when alcohol or formalin are added.

In the remainder of Bloodgood's cases there were no large cysts. Further details will not be given, for his nomenclature is not in line with the general principles which have been laid down. He speaks, for instance, of non-encapsulated adenomatous areas and non-encapsulated cystic adenoma. These terms are undesirable in the discussion of a condition which he himself calls chronic cystic mastitis.

Microscopic Appearance.—It is the extremely varied microscopic picture which has given rise to so many conflicting opinions regarding chronic mastitis. Considered individually the different features are largely meaningless, but when regarded as parts of one process of epithelial hyperplasia or retrogression they become more intelligible. The principal changes are as follows.

1. *A formation of epithelial buds* similar to those seen during the evolution of the breast at puberty. Each bud consists of a solid mass of cells, and on account of its compact nature it stains very darkly. Such a condition may be compared with the fetal adenoma of the thyroid. The parenchyma of the breast seems to be increased, and the appearance is described by some writers as adenomatous.

2. *Cyst formation* is extremely common. In addition to the larger cysts easily seen by the naked eye there are numerous tiny cysts less than a millimeter in diameter. The work of Lenthal Cheatle on the formation of cysts in the breast deserves careful study. He has come to the conclusion that the majority of cysts are formed not from the acini but from the ducts.

3. *Papillary formation* is a characteristic change in many cases, as might be expected from our preliminary considerations. It corresponds to the adenocystic change of Bloodgood and the secondary epithelial hyperplasia of MacCarty. At first the epithelial cells merely multiply and be-

come heaped up in the dilated space, but presently they begin to send finger-like processes inwards (Fig. 343). These fuse together in places so as to form a mass in which there are many spaces, an appearance described by some authors as adenomatous. The interlacing processes may form a beautiful filigree pattern which Lenthal Cheatle describes as laciform or sometimes resembling a cart-wheel. The microscopic picture of epithelial hyperplasia may closely resemble that of exophthalmic goitre or hyperplasia of the prostate.

4. *Pale epithelial cells*, the "blasse Epithelzellen" of the Germans, form a peculiar finding occasionally seen in this condition. The cells are large and clear, with abundant cytoplasm and a vesicular nucleus. Small cystic spaces are filled with these cells, which are desquamated from the

Fig. 343.—Lobular hyperplasia, cystic. Epithelial hyperplasia with papillary processes projecting into cysts. × 125.

lining membrane. They become softened and liquefied, and form the fluid contents of the cysts in Schimmelbusch's disease.

5. *Atrophy of the epithelium* rather than hyperplasia may be the dominant factor. The cells lining the acinus become more and more indistinct, until finally the acinus itself is unrecognizable. As in the case of hyperplasia, the atrophy is not uniform; it may be present in some lobules but not in others.

6. The *connective tissue* undergoes changes as well as the parenchyma, but they are probably not primary in nature. As a rule there is a marked increase. This is best observed in the periductal fibrous tissue, which may be so dense as to suggest a periductal fibroma. Round-celled infiltration around the ducts is fairly common (Fig. 344), especially in those ducts which contain much secretion. This appearance has been taken to indicate that the condition is inflammatory, and is probably responsible for the term chronic mastitis.

The Relation of Lobular Hyperplasia to Carcinoma.—At the present day there is no question more interesting and more vitally important in
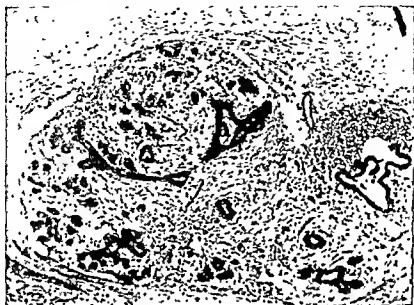
Fig. 344.—Lobular hyperplasia, localised. This section shows the distinction between the fibrous tissues around the ducts and the surrounding stroma; also the dilatation of ducts and the round cell infiltration. × 60

Fig. 345.—Carcinoma of the breast associated with lobular hyperplasia.

breast pathology than the relationship of lobular hyperplasia (chronic mastitis) to carcinoma (Fig. 345). It is interesting because opinions vary

so enormously. It is important because the surgeon has to decide whether or not he will perform a mutilating operation to safeguard his patient against the future possibility of cancer.

The modern tendency is to regard cystic mastitis as a dangerous and precancerous condition, and some surgeons treat any cystic condition in the breast in the most radical manner lest a worse thing should befall their patient. Such an attitude is entirely indiscriminating, and reduces the surgeon to the level of a mere operator. A mutilating operation should not be performed unless there is very good reason for it.

There are two ways of looking at the question, the pathological and the clinical. The epithelial hyperplasia of chronic mastitis need bear no necessary relationship to malignant neoplasia any more than the similar hyperplasia of Graves' disease need bear such a relationship. But we must remember that this hyperplasia is the result of hormonal stimulation, and that, at least in the experimental animal, carcinoma of the breast can be induced by means of estrogenic hormones. Moreover, when the entire breast is carefully examined in chronic mastitis, microscopic evidence is not wanting that epithelial invasion as well as proliferation is not uncommon. From the pathological viewpoint, therefore, there is reason to believe that lobular hyperplasia should be regarded as a possibly precancerous condition.

Some of the clinical evidence is against this view. Bloodgood, and more recently Campbell, are of the opinion that there is no causal relationship between the two conditions. Shields Warren, however, gives the follow-up results after 5 years on 1200 cases of chronic mastitis (lobular

Fig. 346.—Fibrosing adenomatosis. × 22.

hyperplasia) which had been operated on, and compares them as regards cancer incidence with a control group of corresponding age. He finds that the cancer rate for women with preexisting breast lesions is 4.5 times as great as in controls, and between the ages of 30 and 49 it is nearly 12 times as great. Warren concludes that a woman who has had chronic mastitis is in far greater danger of developing cancer, even though all the apparently abnormal tissue has been removed, but once she has passed the menopause (the breast no longer being exposed to hormonal stimulation) there is no greater danger than in any control group. Actively proliferating lesions, such as intraduct papillomas and cysts with papillary epithelium, are of graver import than large cysts with atrophic epithelium. After removal of the diseased tissue the breasts should be examined at regular intervals. This is better than amputation of both breasts, which is not only too radical but too easy for the surgeon. Much, however, depends on the type of lesion and the age of the patient.

Fibrosing Adenomatosis.—Ewing has drawn attention to this condition which he says gives rise, probably more frequently than any other lesion of the breast, to a mistaken diagnosis of cancer. It is commoner in young women. The breast contains a number of hard discrete nodules, the cut surface of which is uniform in contrast with that of carcinoma. The microscopic appearance is described by the name, for there is multiplication of the acinar cells combined with fibrosis, the latter dominating the picture and finally leading to atrophy. There is a tendency for the acini to break up into small groups and clumps of cells. The picture is a characteristic one (Fig. 346). The condition bears no relation to malignancy.

TUMORS OF THE BREAST

Of the true tumors of the breast, 95 per cent fall into two groups, fibroadenoma and carcinoma. The former constitute about 15 per cent, the latter 80 per cent. Every tumor of the breast should be regarded as malignant until it has been proved to be innocent, and the only way to make certain is to make an exploratory incision and judge either from the gross or from the microscopic appearance. An early carcinoma may so resemble a fibro-adenoma clinically as to deceive the very elect.

FIBRO-EPITHELIAL TUMORS

The innocent tumors of the breast are essentially fibro-epithelial overgrowths which are limited by a capsule. Sometimes the fibrous element is
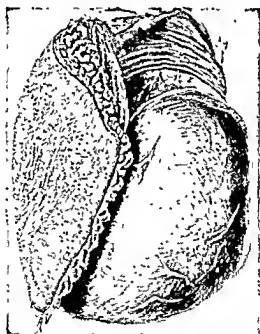
Fig. 347.—Fibro-adenoma of the breast. The encapsulated character of the growth is well shown.

predominant, sometimes the epithelial. The development of cysts will materially modify the character of the tumor.

As a matter of fact it is really difficult to draw a hard and fast line between some cases of chronic mastitis and fibro-epithelial tumors. To the naked eye the capsule is a satisfactory distinguishing feature, but the microscopic picture may be very similar in the two conditions. Three main varieties of fibro-epithelial tumor may be recognized: (1) pericanalicular fibro-adenoma, (2) intracanalicular fibro-adenoma, and (3) duct papilloma.

1. **Pericanalicular Fibro-adenoma.**—This is sometimes called the hard fibro-adenoma of the breast. Rarely attaining a great size, it is well encapsulated by a definite sheath of dense fibrous tissue from which it pops out when the sheath is incised (Fig. 347). Often, however, it is attached to the sheath at one point. Its most notable clinical characteristic is its mobility. So slippery may it be under the hand as to be quite difficult to grasp.

Fig. 348.—Intracanalicular fibro-adenoma. × 175.

On section it is whitish in color, slightly granular, and displays a number of surface markings or splits. It is very firm, but cuts like cartilage and not with the gritty sensation felt in a scirrhous carcinoma. During lactation the fibro-adenoma shares with the rest of the breast in the general hyperplasia.

Microscopically the tumor consists of an overgrowth of both fibrous and epithelial structures. The acini and the ducts appear more numerous than normal, and are surrounded by a stroma of fibrous tissue which varies greatly in density, and which is most marked around the ducts; hence the name periductal or pericanalicular. Although resembling the structure of the normal breast, that structure is never perfectly reproduced. The glandular arrangement is more diffuse, and new lobules are not formed.

2. **Intracanalicular Fibro-adenoma.**—This is the common variety of fibro-adenoma. It is more of a fibroma than an adenoma. When small it

has a moist and succulent appearance which may suggest a medullary carcinoma, but the lack of encapsulation of the latter serves to differentiate. When larger the cut surface may resemble the hypertrophied prostate, and gives the appearance as if many small cauliflower-like masses were enclosed in cysts. These little papillomata can indeed be turned out, but they are found to be attached by a pedicle.

Microscopically there is a remarkable proliferation of connective tissue which projects into the ducts in the form of polypoid masses, producing great elongation and distortion of the ducts, which are usually much

dilated (Fig. 348). The section often does not pass through the pedicle of these polypoid masses, with the result that the dilated duct appears to be crowded with masses of fibrous tissue, each covered by a layer of epithelium invaginated from the duct wall, and separated from one another by a series of branching slits. The connective tissue is so loose in texture that some writers call the condition a myxoma.

These tumors may occasionally attain to a great size, and the larger varieties are said to be liable to sarcomatous transformation.

3. **Duct Papilloma.**—This condition, which bears a certain resemblance to that which has just been described, has had a bewildering variety of names attached to it. Adenocystoma, intracanalicular cyst-adenoma, papillary cystoma, proliferous cyst, villous papilloma, and intracystic papilloma are among the names worth mentioning, for they convey some conception of the nature of the condition.

Fig. 349.—Intracystic papilloma of the breast.

The *gross appearance* varies considerably. In its simplest form the tumor appears as a little papillomatous growth which projects into a dilated duct usually close to the nipple. Whether the dilatation precedes the papilloma or the papilloma the dilatation appears to be as difficult a problem to solve as that of the order of precedence in the case of the hen and the egg. More rarely the papilloma projects into a preformed cyst, in which case it should be called a cyst papilloma (Fig. 349).

At first the nodule consists of a series of epithelial folds, and in its early stages has the appearance of a minute raspberry. As growth proceeds the tumor becomes arborescent or dendritic. The dendrons or villi usually adhere together fairly well, so that the surface appears velvety

rather than villous. The larger specimens distend the duct and become a solid compact mass, although in reality composed of interdigitating papillary processes.

Microscopically the picture is again a varying one. The early stage will show a typical papillary or villous formation, the delicate stroma being covered by a single layer of columnar epithelium. The larger specimens appear to have an adenomatous structure owing to the gland-like spaces formed by the interlacing processes (Fig. 350). It is on this account that such misleading terms as adenocystoma and cystic adenoma have been applied to the condition. The blood vessels are large and thin-walled, so that hemorrhage is common, and a discharge from the nipple, either blood-stained or serous, is one of the most characteristic symptoms.
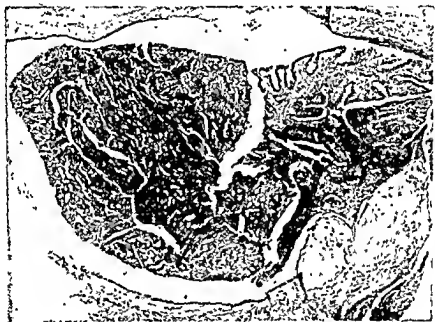
Fig. 350.—Duct papilloma. One of the large lactiferous ducts is greatly dilated by the compressed folds of the papilloma. × 20.

It will be observed that although there is a superficial resemblance between duct papilloma and intracanalicular fibro-adenoma there is this essential difference: in the former the actively growing element is epithelium, whilst in the latter it is fibrous tissue.

There appears to be a definite relation between duct papilloma and duct carcinoma, which will be discussed later.

CARCINOMA

The breast shares with the uterus the distinction of being the commonest site for carcinoma. About 40 per cent of all carcinomas occur in this gland. It is a disease of the involuting breast, being commonest at the time of the menopause, and rare before the age of thirty-five. It may, however, be met with at any time after the twentieth year, and some slow

forms may last for five, ten, or even fifteen years. Spontaneous recovery has been known to occur even after widespread secondary growths have been set up.

As is natural in a complex organ like the breast, the tumor presents marked variations in physical appearance, rapidity of growth, and histological arrangement. As a consequence a great number of names have been applied to the different varieties. Deaver and McFarland give a list of 54 names which they found in the literature. In general terms we may say that the carcinoma may be spheroidal-celled or columnar-celled.

We have seen that in fibro-adenoma the proportion of connective to epithelial tissue may vary markedly, giving rise to corresponding variations in the physical character of the tumor. The same is true for carcinoma. The fibrous tissue is often so abundant that the epithelial hyperplasia appears almost secondary. Such growths are called hard or scirrhous carcinomas. Or the tumor may be highly cellular with comparatively scanty stroma. This is a soft, encephaloid, or medullary cancer. When the epithelial cells are arranged in tubular fashion an adeno-carcinoma results. Colloid degeneration may occur in any of the forms, giving rise to colloid cancer.

The *etiology* of breast carcinoma is shrouded in the same darkness as that of other forms of cancer, but there are two factors of possible importance. The first factor is inadequate drainage of the duct system, as a result of which there is retention of irritating secretions. The ducts may be blocked by plugs of desquamated cells, by developmental anomalies, etc. According to Adair, only 8.5 per cent of patients with cancer of the breast give a normal nursing history. Moreover, it is possible to produce cancer in mice by tying off the ducts to the nipples on one side (Bagg). Oversucking certainly does not act as a predisposing cause, for the most overworked mammary gland in the world belongs to the cow, an animal which never develops mammary cancer. In the human subject the liability to cancer is not increased by the bearing of many children; indeed it appears to be decreased, for the disease is more common proportionately in nulliparous married and in single women. The second possible factor is irregular or abnormal stimuli from the ovaries. If the ovaries be removed from young mice with a strong natural tendency to mammary cancer, the danger of the development of this tumor will be completely averted. On the other hand the injection of ovarian hormone (oestrin) into mice will produce mammary cancer in a high percentage of cases, even in male mice (Lacassagne). It is worthy of note that the development of a tumor is preceded by changes similar to those of cystic mastitis in the human subject, *i. e.*, dilatation of ducts, formation of rysts, the development of papillary processes, and round-cell infiltration. In an extensive investigation of human material Muir found that evidence of the preexistence of malignancy can generally be demonstrated in the ducts or acini before infiltration has occurred. The malignancy is often of multicentric origin and affects groups of cells in a diffuse fashion. In some cases the malignancy may arise de novo without the occurrence of preliminary hyperplasia. Muir found no support for the theory of dual causation, *i. e.*, a diffusely acting hormonal agent leading to hyperplasia followed by another agent (virus) causing focal malignancy.

Perhaps the most remarkable addition to our information of experimental breast cancer is the work of Bittner on the so-called milk factor. If the young of a high breast tumor stock are suckled by mothers of a low breast tumor stock the incidence of breast cancer is greatly reduced. Bittner has even succeeded in extracting the cancer-producing factor in the breast of animals with high spontaneous carcinoma. When this factor was given to animals with a normal incidence of the tumor the incidence rose from 1 per cent to 67 per cent. These startling observations indicate that some extrachromosomal factor can be transmitted in the mother's milk.

Knowledge of the experimental production of mammary cancer may be summarized by saying that there are three possible exciting agents, either extrinsic or intrinsic: (1) a milk inciter (extrinsic), (2) an estrogenic inciter (intrinsic and extrinsic), and (3) an inherited inciter (intrinsic). Two or even three factors may be operative.

In addition to the above, two other factors are often mentioned, namely, trauma and chronic mastitis. There is no proof that trauma bears any etiological relationship to cancer of the breast. It is true that a history of a blow may frequently be obtained, but the breast is a superficial organ which must receive countless blows of which we hear no more. If trauma is a factor to be considered it is likely that the blows are physiological rather than physical. That a physical trauma should produce cancer of the breast is contrary to the dictum that the stimulus to cancer must be of the same type as that to which the particular tissue is biologically best adapted to respond with proliferation.

The relationship of lobular hyperplasia (chronic mastitis) to carcinoma has already been discussed on page 524. The former condition, which is undoubtedly the result of hormonal imbalance, is a state of epithelial instability and overactivity which may develop into carcinoma, perhaps owing to the operation of additional factors.

The average duration of life in untreated cases, as shown by a report by Janet Lane-Claypon to the British Ministry of Health, is a little more than three years. Of cases which had received surgical treatment by the modern complete operation, 52 per cent were alive and well after three years and 30 per cent after ten years. Many of these were rather advanced cases. Of patients subjected to early operation—i. e., before the disease had extended beyond the breast itself—94 per cent were alive and well at the end of three years and 87 per cent at the end of ten years. Lewis and Rienhoff analyzed the results of operations for cancer of the breast at the Johns Hopkins Hospital from 1889 to 1931, and came to the conclusion that the great majority of cases will succumb to the disease. It is true that many patients remained free from clinical cancer for many years, but these authors doubt if anyone is cured in the pathological sense. A clinical cure may follow operation, but regional microscopic metastases may be found years later.

It is the custom to recognize several variations of breast carcinoma to which the names of scirrhous, medullary, and adenocarcinoma have been applied. As this terminology is so well established it will be followed here, but it must be realized that two or even three of these may occur in the same breast. One block may show a scirrhous condition, whilst another a

few centimeters away may provide a perfect example of a medullary carcinoma.

As the scirrhous form of carcinoma is by far the most common and important, the general characteristics of cancer of the breast will be considered with reference to this variety.

Scirrhous Carcinoma.—Clinical Features.—A scirrhus begins as a hard nodule which can best be appreciated with the flat of the hand. The commonest site is the upper and outer quadrant, but it may commence in any part of the breast. It is not confined to one lobe, but extends in an irregular manner. It becomes fixed to the deep fascia and later to the skin. There may be local flattening or general shrinkage of the breast; local flattening suggests carcinoma, whereas local prominence suggests a benign tumor or cyst. The skin may become ulcerated (Fig. 351), so that the tumor projects on the surface as a fungating mass (Fig. 352). Slight dimpling
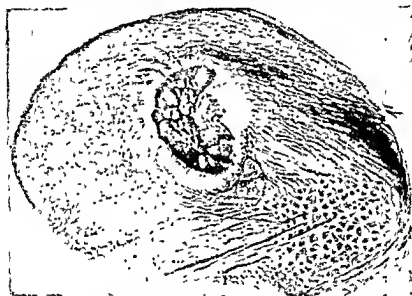
Fig 351.—Carcinomatous ulcer of breast.

of the skin due to lymphatic edema occurs at an early stage. Involvement of the large milk ducts is responsible for fixation and later actual indrawing of the nipple. Retraction of the nipple is very suggestive of early duct carcinoma or advanced carcinoma starting elsewhere. Although more slowly growing than the medullary form the end results are worse instead of better. The axillary, subclavian, and supraclavicular glands may be enlarged and hard, but neither painful nor tender. It cannot be too strongly emphasized that glandular enlargement is not characteristic of the early and operable stage of the disease, and its absence should never be accepted as a sign of diagnostic value. *Most of the classical symptoms such as fixation to the deep fascia and retraction of the nipple are late signs due to the fibrosis which accompanies the epithelial overgrowth, and are therefore not present in the early stages.*

After operation there may be troublesome swelling of the arm due to edema. This may be caused by lymphatic obstruction or venous obstruction or both. Venous obstruction is the commoner. There may be pressure on the axillary vein by recurring tumor or as the result of scar formation. The obstruction can be demonstrated by venography using thorium dioxide. Sufficient collateral circulation may develop to take care of the obstruction.

Spread.—A knowledge of the methods of spread is essential to the surgeon because no operation is of avail unless it removes not only the primary growth but the whole infected area. The disease spreads locally and at a distance. The local spread is by infiltration and extension via the
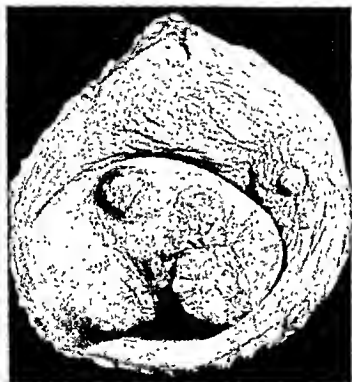
Fig. 352.—Fungating carcinoma of the breast.

lymphatics. Distant spread is by embolism and transcelomic transplantation. For many years the views of Sampson Handley have dominated the teaching and practice of surgeons. According to Handley lymphatic permeation is the all-important method of spreading the disease not only locally but also at a distance. Gradually opposition to the doctrine of lymphatic permeation has begun to make itself felt.

1. *Infiltration.*—The cancer cells extend outwards from the primary growth, and infiltrate the tissue spaces between the fat cells and bundles of fibrous tissue. These interspaces may be regarded as lymph spaces, but they are not lined by endothelium. The process of infiltration although earliest in point of time, is slow and of relatively little importance as a means of general dissemination. The familiar appearance of cancer cells

arranged in columns in single file is an indication of the infiltration of tissue.

2. *Lymphatic Spread.*—It is possible for cancer cells to spread along lymph channels in two ways. They may either grow along the vessels by a process of multiplication or they may be carried along the lymphatics in the form of emboli. The infection of the axillary lymph nodes from the primary tumor is an example of embolic spread. The first process is indissolubly associated with the name of Sampson Handley, whose work on what he terms lymphatic permeation has been generally accepted for many years. According to Handley, when the cancer cells enter a lymphatic they commence to grow along it, even "up-hill" in a direction contrary to the lymph flow. The cells grow steadily outwards in a centrifugal fashion, forming a circle of ever-widening radius, of which the center is the primary focus. Within this circle healing takes place owing to a connective tissue reaction, round-cell infiltration, and perilymphatic fibrosis. The healing process fails to overtake the actual growing edge, which is only a few millimeters in width. In this way the ring of permeation at any one time is not a disc but a ring, so that the spread may be likened to that of annular ringworm. Handley considers that the circle of extension may finally attain a diameter of two feet, involving the cranium above, the vertebral column behind, and the groin below. Distant bony involvement of the vertebrae, the skull, the humerus, and the femur is explained on this basis. It is the upper end of the proximal bones of the limbs which show the secondary growths. The bones distal to the elbow and knee are very rarely involved. All this is in accordance with the theory of permeation.

Fitzwilliams and others have attacked the theory of lymphatic permeation. This method of spread, it is pointed out, should hold for other forms of carcinoma as well as cancer of the breast. But is there evidence of this? We do not find ripples of extension from cancer of the lip and tongue, cancer of the bowel, cancer of the anus. In the last named we would expect to find nodules in the buttocks and the thighs, but such is never the case. In cancer of the bowel the disease should spread up and down the bowel along the lymphatics, but it does not. In all these cases the spread is by lymphatic embolism, not by permeation. According to Fitzwilliams cancer of the breast spreads by embolism via the lymphatics and the blood stream. The reason why the proximal end of the femur and humerus is the common site of metastases and not the distal bones of the limbs has been explained by Piney. The red marrow, rich in blood vessels, fills the medullary cavity of the long bones in childhood, but after puberty it is replaced by the relatively avascular yellow marrow. The red marrow persists, however, in the upper end of the humerus and the upper end of the femur as well as in the vertebrae, ribs, and sternum, all of which are common sites for secondary growths in carcinoma of the breast, for it is in the richly vascular red marrow that the emboli of tumor cells are naturally arrested. The bones distal to the elbow and knee are very rarely involved. All this is in accordance with the theory of permeation.

Fraser, in his study of cancer of the breast by the whole section method, found that the heaviest involvement of the lymphatics was in the im-

mediate proximity of the original growth both in the early and in the advanced cases. There was no evidence of the fibrosis and destruction of cancer cells which Handley has described. His impression is that the lymphatic extension within the breast is on an embolic rather than a permeation basis.

Handley's most important contribution, however, has been not so much the theory of permeation as a demonstration of the routes along which extension occurs, and this has been amply confirmed. The cancer cells pass downwards in a vertical direction through the thickness of the breast to the plexus of lymphatics which lies upon the deep fascia, and it is along the planes of the deep fascia and the muscular aponeurosis that the principal spread takes place.

Nodules may appear in the skin, particularly after removal of the tumor. This is not due to spread along the lymphatics of the skin, but to infection from the fascial plexus. The lymphatics of the skin begin in the dermal papillae as blind end-sacs, extend downwards at right angles to the surface through the deeper layers of the dermis and the underlying subcutaneous fat, and discharge into the lymphatic plexus which lies on
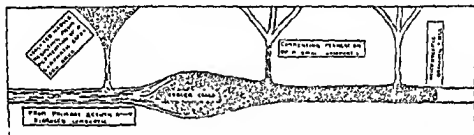
Fig. 353.—Diagram illustrating the permeation of a lymphatic of the breast by carcinoma cells, and showing the distension of the lymphatic, the formation of a skin nodule, and the lymphatic fibrosis. (After Sampson Handley.)

the deep fascia. The cancer which spreads along the deep fascia may thus grow up along some of these lymphatics, and here and there blossom out into skin nodules (Fig. 353).

The obliteration of the deep lymphatics by the defensive fibrosis may give rise to *lymphatic edema* of the skin. There is swelling of the corresponding areas of skin, but those points which are anchored by the hair follicles are unable to participate in the general expansion, so that numerous little dimples are formed, giving an appearance not unlike that of the skin of an orange, this condition known as "pig-skin" (Fig. 354) or "peau d'orange." Fraser considers that this condition, known clinically as *cancer en cuirasse*, a pachydermatous condition of the skin supposed to indicate cancerous infiltration, is merely an edema of the papillary structures of the skin due to subcutaneous lymphatic obstruction. Obstruction of the larger lymphatic vessels of the area may cause a brawny swelling and induration similar both in appearance and causation to elephantiasis.

In the course of extension the carcinoma cells may invade the body cavities, both pleural and peritoneal. The pleural cavity may be invaded along lymphatics which pierce the pectoral and intercostal muscles and

communicate with the subpleural lymphatics. The peritoneal cavity is invaded from the abdominal wall. Stiles has shown that the lower and inner margin of the breast is only one inch from the interspace between the ensiform cartilage and the seventh costal cartilage. In this region the lymphatic plexus in the epigastric aponeurosis is only separated from the subperitoneal lymphatics by the linea alba, so that when the cancer cells have extended one inch beyond the breast they have merely to pass through a single layer of fibrous tissue traversed by lymphatics. It is not surprising, therefore, that through this weak spot cancer frequently reaches the peritoneum even before it has succeeded in penetrating the pleura.

The lymphatic spread may be summarized as follows. (1) To the axillary, infraclavicular and supraclavicular groups; from these to the cervical nodes. (2) To the anterior mediastinal nodes via lymphatics accompanying the perforating branches of the internal mammary artery, thence to
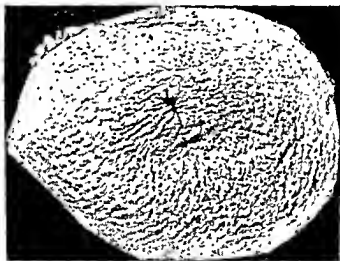
Fig. 354.—Carcinoma of breast showing indrawing of nipple and condition of pig-skin.

the posterior mediastinal and bronchial nodes. (3) To the pleura via the intercostal lymphatics. (4) To the peritoneum via lymphatics passing through the rectus and along the falciform ligament. (5) To the opposite breast and axillary nodes by a cross lymphatic connection between the two breasts. (6) To the skin directly and via the fascial plexus of lymphatics.

3. *Transcelomic Implantation.*—Numerous fine anastomoses connect the lymphatic plexuses of the deep fascia with the subendothelial plexuses of the pleura and peritoneum. The cancer cells, having reached the latter plexuses, burst the lymphatics, escape into the serous cavities, and are distributed throughout these cavities by gravity and by visceral movement. They become implanted at various points on the serous surface of the viscera, where they set up secondary growths, with a resulting embolic infection of the glands which drain that area. Gravity plays a part in this dissemination, so that the diaphragm and the pelvic viscera,

particularly the ovaries, are often the seat of metastases. Invasion of the abdomen without corresponding invasion of the thorax occurs in about 15 per cent of cases. If embolism by the blood stream was responsible for the metastases the cancer cells would all require to pass through the lungs first before reaching the abdominal viscera.

The liver is involved far more frequently than any other abdominal organ. Its method of infection is interesting. Cancer cells entering the peritoneal cavity may be implanted directly on the surface of the organ. Such a method would hardly explain the frequent occurrence of nodules scattered throughout the substance of the liver. The usual route appears to be along the lymphatics of the falciform ligament to the portal glands, whence the disease permeates the lymphatics of the portal tracts and sets up secondary growths throughout the liver.

Cancer, like empyema, apparently has great difficulty in penetrating the diaphragm from above downwards, possibly on account of the strong lymph current which flows in the reverse direction. The crural lymphatics, however, unlike those of the rest of the diaphragm, drain into the lumbar

Fig. 355.—Scirrhous carcinoma of breast. The main tumor is situated below a much indrawn nipple. There are several smaller outlying masses the result of lymphatic spread.

glands instead of those of the thorax. In this way retroperitoneal infection may occur, with the formation of metastases in the kidney, the adrenal, and the lumbar vertebrae.

Spread by the Blood Stream.—It has already been shown that many of the metastatic deposits which in the past have been attributed to lymphatic permeation are now recognized to be due to blood spread. The organs most frequently found to be involved by metastases at autopsy are lungs, liver, bones, adrenals, spleen and ovaries in that order. Radiological examination of the skeleton might bring the bones to the top of the list. The adrenals, spleen, and ovaries are more often the site of metastases than is usually realized.

Gross Appearance of Scirrhous Carcinoma.—The breast is small, hard, and flattened. The tumor is firmly adherent to the surrounding tissue, and sends radiating processes out into the fat (Fig. 355). When incised it cuts with the peculiar gritty sensation of an unripe pear, and often presents the white striations seen in that fruit, these being bands of fibrous tissue. The cut surface is of a greyish color, contrasting with the dense

when incised it feels hard, but neither tough nor gritty. Carcinoma is irregular in shape, indefinite in outline, firmly adherent to the surrounding fat, densely hard, grey in color but not homogeneous looking, cuts with a peculiar gritty feel, and "cancer juice" may be scraped from the surface.

Carcinoma may arise in a breast already the seat of lobular hyperplasia, so that the two conditions frequently co-exist. It may also be associated with fibro-adenoma, but does not arise from conversion of that tumor into a malignant growth.

The less common varieties of cancer of the breast may now be briefly considered.

Medullary or Encephaloid Carcinoma.—When the glandular proliferation is marked in comparison with that of the connective tissue, a soft, rapidly growing tumor results, which invades the skin, ulcerates, and appears on the surface as a large fungating mass. Unlike a scirrhus the tumor
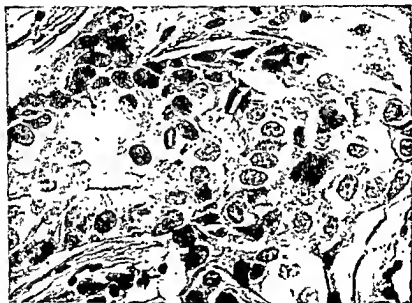
Fig. 357.—The cells of a medullary carcinoma of the breast; one mitotic figure. × 500

is very friable so that little pieces can be picked out with a knife. The axillary glands enlarge rapidly, and the course of the disease is comparatively quick.

Microscopically, masses of large, rounded epithelial cells, much paler than those of a scirrhus, are separated by scanty and relatively delicate stroma (Fig. 357). Mitotic figures are numerous, and degenerations are common and extensive.

Acute carcinoma is medullary in type but more diffuse in distribution. There is rapid dissemination of the growth throughout the breast and in the skin. It generally develops during lactation; *i. e.*, lactation makes the condition acute. As the breast is inflamed and swollen, and the skin hot and red, the condition may be mistaken for acute mastitis. The appearance of secondary nodules in the skin is diagnostic. Death results within three months.

Adenocarcinoma.—This is an uncommon form of breast cancer, which is unfortunate, for it is of relatively low malignancy and may remain localized for a long time. It is possible that some of these tumors arise from sequestrated sweat glands. Axillary node involvement is exceptional. The tumor forms a bulky mass in the breast, and it is sometimes known by the convenient name of *bulky adenocarcinoma,* convenient because it serves to distinguish it *from other conditions* to which the name adenocarcinoma is applied. It is soft in consistency. Microscopically it consists of gland spaces surrounded by columnar epithelium. In the late stages there may be ulceration of the skin over a large fungating tumor.

Duct Carcinoma.—Two types of growth have been included under this heading. (1) A *papillary tumor* which distends one of the large ducts near the nipple. It is probable that this type usually arises from a duct
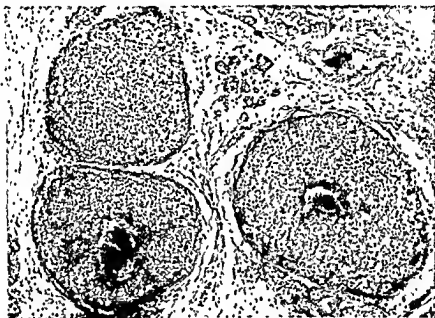
Fig. 358.—Intraduct carcinoma of the breast (comedo form)· The tumor cells are confined within the ducts. × 85.

papilloma. Owing to fusion of the papillary processes a gland-like formation may be produced, on which account the tumor has been called cystadenocarcinoma. They usually remain localized for a considerable time, but sometimes invasion occurs early in the disease, and there may be metastases both in the regional lymph nodes and in distant organs. A bloody discharge from the nipple is the most characteristic feature. (2) *Intraduct carcinoma* (Fig. 358), a condition in which the smaller ducts are filled with closely packed epithelial cells, which eventually break through the limiting membrane and invade the surrounding tissue. This is what Bloodgood calls the comedo form of adenocarcinoma, because worm-like casts can be expressed from the cut surface, leaving little cysts which represent the dilated ducts. When the cells are still confined within the duct it may be very difficult to decide if the condition should be called

a carcinoma, for the epithelial hyperplasia of chronic mastitis gives a very similar picture.

Sweat Gland Cancer.—The mammary gland and the sweat glands have a common origin from a primitive tubular type of epidermal gland. Structures which are apparently sweat gland tubules occur in the normal breast and anastomose with the lacteal ducts. They are distinguished by marked eosinophilia of the cytoplasm and an inner layer of high columnar cells with a tendency to form intratubular and intracystic ducts. Certain carcinomas of the breast, usually situated at the periphery of the organ, may display these characters and are known as sweat gland carcinoma. Their behavior is the same as that of ordinary breast cancer.

Paget's Disease of the Nipple.—This interesting condition, first described by Sir James Paget in 1874, is one which has aroused great discussion for many years, and a variety of views have been held as to its nature.

Paget's original description of the clinical condition is one of those masterpieces which were commoner in the nineteenth than the twentieth century. "The patients were all women, various in age from 40 to 60 or more years, having in common nothing remarkable but their disease. In all of them the disease began as an eruption on the nipple and areola. In the majority it had the appearance of a florid, intensely red, raw surface, very finely granular, as if nearly the whole thickness of the epidermis were removed; like the surface of a very acute diffuse eczema, or like that of an acute balanitis. From such a surface, on the whole or greater part of the nipple and areola, there was always copious, clear, yellowish, viscid exudation. The sensations were commonly tingling, itching and burning, but the malady was never attended by disturbance of the general health."

It commences as an intractable eczema of the nipple, but sooner or later, usually within two years but occasionally not for as long as ten, a carcinoma appears in the breast, frequently at some distance from the nipple. The eczematous area is usually bright red and inflamed-looking, with a finely granular surface (Fig. 359). The surface may be moist and weeping, or dry and scaly. An excellent color plate of an advanced phase of the clinical condition will be found in Cheatle and Cutler's monograph on the breast.

The *microscopic picture* presents three features: (1) epidermal hypertrophy, (2) Paget cells, (3) subepidermal round cell infiltration.

1. Epidermal hypertrophy, before ulceration has taken place, is a constant feature. The epidermis may be two or three times the normal thickness, and the epidermal papillae are increased both in depth and width.

2. Paget cells are large, clear, vacuolated cells with small pyknotic nuclei. They look like clear spaces punched out of the epidermis (Fig. 360). They may lie singly or in small groups in the deeper layers of the epidermis. The vacuolated appearance is due to hydropic degeneration. The question of whether they are normal epidermal cells which have undergone degeneration or whether they are tumor cells is discussed below.

3. The superficial part of the dermis shows a marked infiltration with round cells and plasma cells.

In addition to these changes in the neighborhood of the nipple lesion there are proliferative changes in the epithelium of the breast which are discussed in the next section.

Nature of the Disease.—There has been much difference of opinion on the course of events in Paget's disease, and even on the nature of the lesion of the nipple. It can be stated definitely that the eczematous condition of the nipple is due to a cancerous lesion, albeit of low malignancy and very slow growth, so that the axillary glands are not involved. It is more difficult to say whether the Paget cells represent malignant cells or normal epithelial cells which have undergone hydropic degeneration as the result of lymphatic obstruction. The very fact that the cells are so degenerated makes the decision all the more difficult. The chief point of importance is that the epidermal cells may be malignant from the cytological standpoint (irregularity of size and staining, hyperchromatism, mitoses, etc.), and yet histologic evidence of malignancy (invasion) may be lacking.

Fig. 359.—Paget's disease of the nipple.

Fig. 360.—Paget cells. × 250.

The relationship of the skin lesion to the carcinomatous tumor of the breast which develops sooner or later has long been the subject of dispute. It seems probable that in the majority of cases the disease commences as an intraduct carcinoma in the ducts of the nipple, which spreads upwards into the skin and downwards into the breast (Muir). As Inglis points out, the duct cancer which spreads from the point of origin is a special variety and is essentially different from ordinary duct cancer. The special quality of the cells is in the intraepithelial character of their spread. They extend along the duct not as a solid column but in the form of a hollow cylinder. They also penetrate between the epithelial cells of the epidermis. These infiltrating cells undergo hydropic degeneration and assume the clear vacuolated appearance of Paget cells. If the cancer cells

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remain confined to the duct the malignant character of the condition may be overlooked, and clinically no tumor can be palpated. Eventually, however, they may penetrate the wall of the duct, and give rise to an infiltrating carcinoma of the ordinary type. In some of my own material I have received the strong impression that the malignant condition in the skin of the nipple is an independent process, and that from this primary focus the disease may extend into the underlying ducts. Inglis reports cases which appear to bear this out. There is a third possibility that a carcinogenic agent may act both on the skin of the nipple and on the epithelium of ducts at a distance. This is the view sponsored by Lenthal Cheatle, and the reader will find a full discussion of the whole subject in Cheatle and Cutler's book on Tumors of the Breast as well as in the monograph by Inglis.

Radiation in Cancer of the Breast.—Cancers of the breast as a class tend to be radioresistant. It must be remembered, however, as Lee points out, that carcinoma of the breast is not one disease but a group of diseases which differ in their gross anatomy, their pathological histology, and their clinical course, as well as in their radiosensitivity. It is therefore unscientific to group them together in determining the degree of their sensitivity, as has been done in the past. Each group must be investigated separately. Scirrhous carcinoma is highly radioresistant, as are most tumors that are markedly desmoplastic. The highly cellular medullary form may be quite sensitive to radiation. Adenocarcinoma and duct carcinoma do not respond well. The rapidly growing anaplastic forms respond best, but as they metastasize at an early date they have the worst prognosis. The large amount of fat in the breast is a formidable barrier to radiation, and outlying islands of tumor cells are very apt to escape unharmed. Microscopic sections of the whole thickness of the breast show that the lymph nodes on the anterior surface of the pectoral muscles are involved in over half the cases of scirrhous carcinoma at the time of operation; such nodes are hard to reach with radiation alone.

The effects of external radiation are mainly vascular; there is a productive arteritis with thrombosis, and secondary degenerative and atrophic effects on the tumor cells. Interstitial radiation acts directly on the tumor cells, producing ballooning, hydropic degeneration, a tendency to squamous metaplasia, necrosis and sloughing.

Bloody Discharge from the Nipple.—There is a wide divergence of opinion as to the significance of a blood-stained discharge from the nipple, and opinions as to the correct treatment differ correspondingly. It is first necessary to determine if the discharge really contains blood. The chocolate-colored discharge which sometimes occurs in chronic mastitis is apt to be described by patients as bleeding from the nipple. Microscopic examination of a stained smear of the discharge will at once determine if red blood cells are present. Transillumination of the breast is another useful method of examination. A bleeding tumor, in which there is usually a cyst filled with blood, is opaque to transmitted light.

In a series of 108 cases of bleeding from the nipple examined by Adair, 47.2 per cent were due to carcinoma and 52.8 per cent to a benign lesion. The *benign* lesion was nearly always a duct papilloma or papillary cyst-adenoma. A small tumor is present within the areola or behind the nipple,

and the ampulla of the duct is distended to form a cyst. Bleeding readily occurs from the terminal capillaries of the fragile papilloma, just as in papilloma of the bladder. Pressing on the nipple serves to start the discharge. In rare cases the lesion may be a chronic mastitis. The *malignant* lesion is a duct papilloma which has become malignant after a number of years, or a duct carcinoma which may be at some distance from the nipple. In the latter case the blood is likely to be dark and stagnant.

Sarcoma.—Although by no means a common tumor, sarcoma of the breast is not so rare as used to be supposed. The most common type is the adenosarcoma. This represents the malignant form of fibro-adenoma. About half the cases represent the malignant transformation of a long-standing fibro-adenoma. In one of my cases a typical fibro-adenoma was removed from the breast, and three years later a typical adenosarcoma was removed from the same breast. The other sarcomas of the breast show no glandular arrangement and are of the spindle cell type.
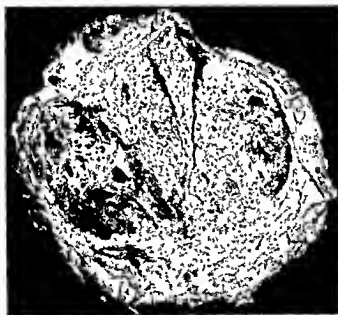
Fig. 361.—Angioma of the breast.

Sarcoma occurs during the same age period as carcinoma, but differs from that disease in its rapidity of growth, and in the great enlargement of the breast which it produces. Lymph-node involvement is much less common than in carcinoma, but secondary growths are found in the lungs and other viscera. In the cases which I have examined it has usually been possible to make a correct diagnosis from the appearance of the gross specimen. The cut surface presents a homogeneous appearance like that of fish-flesh, and shows none of the fibrous strands and yellow areas of necrosis so characteristic of carcinoma. Microscopically the tumor is composed of spindle cells, which in the adenosarcoma are arranged around acini and ducts as well as in a diffuse fashion. The normal glandular structure has disappeared.

Many other tumors such as lipoma, myxoma, chondroma, and chondrosarcoma may occur in the breast. They are very rare and do not call for any special consideration. Osteogenic sarcoma is another rare tumor, which presents the same microscopic picture as osteogenic sarcoma of bone with formation of bone and cartilage, but the tumor is usually sharply circumscribed. A somewhat commoner tumor is the angioma. This may be no larger than a hazel nut, but I have seen one the size of half a grapefruit (Fig. 361). Rarely in man but frequently in the dog malignant *mixed tumors* occur which con-

tain not only epithelium but also cartilage and bone, myxomatous and osteoid tissue (Allen). The epithelial cells become isolated in a mucoid matrix, and it is from this matrix that the cartilage seems to be formed.

FAT NECROSIS

An occasional cause of a lump in the breast which is easily mistaken for carcinoma is the condition known as fat necrosis. This is sometimes called traumatic fat necrosis, because the development of the lesion is often preceded by some form of trauma, but in about half the cases there is no such history. A similar lesion may occur in the fat in other parts of the body. The condition is essentially benign.

Gross Appearance.—The affected area is opaque, of a white, waxen appearance and may show one or more cysts containing liquefied fat;
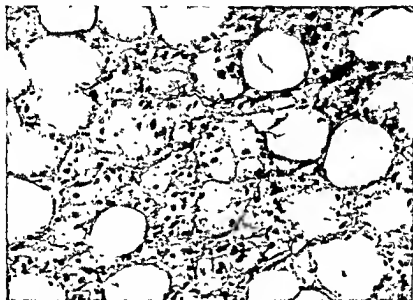
Fig. 362.—Fat necrosis of the breast. The large clear globules represent normal fat. The cloudy cells in the center represent necrotic fat. × 200.

or the center may simply be somewhat diffluent. The area is more or less encapsulated; at least there is no evidence of infiltration. The cicatricial contraction and the yellow points and streaks of carcinoma are not observed. Although to a superficial examination there may be a resemblance between the gross appearance of carcinoma and traumatic fat necrosis, a careful study will reveal essential differences. It is possible to make a correct diagnosis on the operating table from the gross appearance.

Microscopic Examination.—In the early lesions the appearance is easily recognized, for the normal clear fat cells are cloudy and opaque due to what is really a saponification rather than a true necrosis (Fig. 362). Fatty acid crystals may be present. The fatty acids combine with the lime salts of the plasma. The necrotic and liquefied areas are surrounded by abundant newly formed connective tissue, so that the picture

is one of chronic productive inflammation in the fat. Giant cells of the foreign body type are numerous. The blood vessels show an obliterating endarteritis and a perivascular infiltration with lymphocytes.

CYSTS

Cyst formation is of common occurrence in the breast. It is customary to draw up elaborate classifications of cysts of the breast, but little is to be gained from this practice. The important cysts have already been considered in discussing chronic mastitis. We have distinguished the single blue-domed cysts occurring in younger women, and the diffuse multiple small cysts seen in elderly women. Occasionally the breast is riddled with larger cysts—the classical cystic disease of the breast.

Very many of the cysts of the breast, particularly those known as involution cysts and the cysts of chronic mastitis, are regarded as retention cysts due to obstruction of

Fig. 363.—Tuberculosis of breast. The condition was mistaken clinically for carcinoma.

the ducts from fibrosis. There is no proof of this theory; no one has ever demonstrated a duct being strangled by fibrous tissue. It is much more probable that the cyst formation is due to epithelial hyperplasia followed by involution.

The relation of cysts to such tumors as duct papillomas and intracanalicular fibroadenomas has already been dwelt upon.

A *galactocele* is a very rare condition in which a large cyst containing milk arises during lactation. It is situated close to the nipple, and pressure upon it causes milk to exude from the nipple. The cause of the obstruction is unknown.

Hydatid cysts are of such rare occurrence that they need only be mentioned.

TUBERCULOSIS

This is uncommon but not rare. In the early stage a firm mass is present, which may readily be mistaken for carcinoma. Softening occurs later, and tuberculous sinuses may be formed (Fig. 363). The microscopic picture is characteristic.

SYPHILIS

This is rare. Although a chancre of the nipple may occur, the important lesion is the tertiary one, as it may be mistaken for carcinoma. There may be a localized gumma, or a diffuse induration with no really characteristic microscopic appearance, and therefore very difficult to diagnose.

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DISEASES OF THE ARTERIES AND VEINS

ACUTE ARTERITIS

For practical purposes acute inflammation of an artery, as of a vein, may be regarded as being bacterial in origin. It is true that the cut end of an artery becomes the seat of a plastic inflammation, but from the surgical standpoint the above statement may be generally accepted. This infection may reach the affected segment of vessel from without or from within. The first form commences as a periarteritis, the second form as an endarteritis.

1. *Acute Purulent Periarteritis.*—At first sight it appears somewhat remarkable that an artery, which traverses an abscess cavity and is constantly bathed in pus swarming with virulent organisms, does not in every instance develop an acute inflammation. As a matter of fact such an inflammation is by no means common, the reason being that the walls of the vessels are nourished by vasa vasorum which are separate from the main trunks, so that the vessel wall is able to offer very considerable resistance.

Not infrequently, however, this resistance is broken down, and the walls of the vessel become acutely inflamed and infiltrated with pus cells. The elastic lamina offers the stoutest resistance, but when it gives way severe and fatal hemorrhage may result. There may be a few small preliminary hemorrhages into a draining abscess before the final flood.

This accident is especially common in the neck in connection with peritonsillar abscesses which threaten the carotid artery. A tuberculous abscess of the lung may erode a branch of the pulmonary artery, and the cold abscess of Pott's disease may do the same for the vertebral artery.

Secondary hemorrhage, fortunately rare in these days of asepsis, is due to a periarteritis. The conditions for trouble are ideal. The vessel has been traumatized and separated from its surroundings, the inner and middle coats are lacerated, and any ligature is buried in the outer coat. The protecting thrombus which forms soon becomes infected and disintegrates, and it is then only a matter of time before the inflamed and weakened vessel gives way.

2. *Embolic Endarteritis.*—When an infected embolus lodges in an artery the result is a septic endarteritis. The source of the embolus is usually either an inflamed vein or an ulcerative endocarditis. The results have already been described in the previous section. Of these the most important are: (1) a septic thrombosis, (2) the formation of metastatic abscesses, and (3) the production, through local weakening of the vessel wall, of a small acute mycotic aneurism, which, giving way, may lead to severe and even fatal hemorrhage. Cerebral hemorrhage, as already remarked, may in this way complicate ulcerative endocarditis. If the

artery blocked belongs to a terminal circulation the usual phenomena of infarction will result. The infarct, of course, will be a septic one.

PHLEBITIS

Inflammation of a vein has many points in common with inflammation of an artery. Thrombosis, however, is much more frequently associated with the inflammation, so frequently, indeed, that the condition is often referred to as thrombophlebitis. The thrombosis advances ahead of the inflammation. On this account hemorrhage is rare compared with the similar condition in arteries.

The relation of phlebitis to thrombosis has already been discussed on page 83, and need not be repeated here. Low grades of inflammation, non-suppurative in type, may be associated with thrombosis, in which cases the condition deserves to be called thrombophlebitis. It must be realized, however, that most thrombi occurring in veins are not dependent on inflammation of the vein wall, and in such cases the name venous thrombosis should be used, not thrombophlebitis.

Suppurative Phlebitis.—From the viewpoint of the surgeon this is by far the most important variety of phlebitis. It is caused by pyogenic bacteria. The infection, in the great majority of cases, invades the vein from without, the phlebitis being preceded by a cellulitis of the surrounding tissue. This cellulitis may extend along the course of the vein, so that the phlebitis has every facility for extension.

The wall of the vein is infiltrated with leucocytes, just as in acute arteritis. Thrombosis rapidly occurs. The clot softens and mingles with the pus from the vessel wall. Hemorrhage is not common for reasons already discussed.

In other cases the inflammation may be due to pyogenic bacteria carried directly to the wall of the vein, with the early formation of a septic thrombus. Such a condition commences as an endophlebitis rather than a periphlebitis, and is accordingly much more in line with acute arteritis which is so frequently dependent upon the impaction of a septic embolus in the lumen of the vessel.

Suppurative phlebitis is seen in any part of the body following operations or secondary to purulent inflammation. The condition has every inducement to spread along the vein, a spread which may prove fatal unless the part is opened up and the inflamed and thrombosed vein tied off from the general circulation.

Some of the most notable examples of suppurative phlebitis are as follows: phlebitis of the lateral sinus following acute inflammation of the middle ear, and threatening to extend down the internal jugular vein; phlebitis of the facial veins following a boil or carbuncle of the upper lip, extending through the ophthalmic veins to the cavernous sinus; phlebitis of the hemorrhoidal veins following operations on the hemorrhoidal plexus or the rectum; phlebitis extending from the appendix to the portal vein; phlebitis of the mesenteric veins following suppurative conditions of the intestine and threatening gangrene of the bowel from the obstructive thrombosis; thrombosis of the pelvic veins following puerperal sepsis or operations on the uterus and appendages, spreading along the veins of the broad ligament to the external iliac and femoral veins; phlebitis of

the veins of the leg in cases of varicose veins with ulceration and other septic conditions in that region.

ARTERIAL DEGENERATIONS

The degenerative conditions which may affect the arteries are of medical rather than surgical interest, but the effect of these degenerations is sometimes to produce conditions which have to be treated surgically, so that a brief review is necessary. The common name, arteriosclerosis, is a source of some confusion. It includes three groups: (1) atheroma, (2) medial or Monckeberg's sclerosis, (3) diffuse hyperplastic sclerosis. The term arteriosclerosis is sometimes confined to the third group.

Atheroma.—This is a degenerative lesion affecting principally the intima of the aorta, the cerebral and the coronary arteries. The change begins as a deposit of lipoids in the deeper layers of the intima, and a localized nodular lesion is formed which projects into the lumen and in

Fig. 364.—Mönckeberg's sclerosis with calcification of the middle coat of the artery. The lumen is obliterated by a thrombus.

the case of the small vessels may narrow it considerably. Softening, ulceration and calcification of the thickened patch is common, especially in the aorta. The media may show secondary degenerative changes.

Monckeberg's Sclerosis.—This is also called medial sclerosis and annular calcification, because calcified rings of lime are formed in the fibrosed middle coat of the medium sized and smaller peripheral vessels (Fig. 364). The medial and the intimal forms of degeneration are often combined causing a narrowing of the lumen which may sometimes amount to complete occlusion, and the peripheral circulation may be interfered with to such an extent that a slight injury may cause gangrene of the part. The changes are most pronounced in old persons, and the dry gangrene produced is known as *senile gangrene*. Similar lesions may occur in dia-

betics at an earlier age, and the *diabetic gangrene* which results occurs the more readily on account of the lowered tissue resistance produced by metabolic toxins and the presence of sugar. Bacterial infection is therefore common, and the gangrene tends to be of the rapidly spreading and moist type.

Diffuse Hyperplastic Sclerosis.—In this form, which is best seen in the smaller arteries to the viscera (kidney, spleen, pancreas), there is a sclerosis and thickening of all the coats, together with a splitting up of the internal elastic lamina. It is often associated with arterial hypertension.

Thrombo-angiitis Obliterans.—This condition is known as Buerger's disease because Buerger, while not the first to describe it, showed that the lesion in the vessels is inflammatory and *not* degenerative. The symptoms are due to the after-effects of the disease; there may be little clinical evidence of the active phase of the process.

The age, sex and race incidence are noteworthy. It is a phase of young males, being extremely rare in women, and seldom developing after the age of forty. In North America it is usually seen in young Russian and Polish Jews (on account of which a relationship with typhus fever has been suggested), but Gentiles may suffer and even Scotsmen are not immune. It is usually confined to the vessels of the legs, but the arms are often affected.

The cause is unknown, but is probably some form of infectious agent. Non-hemolytic streptococci have been cultured from the blood, and injection of these organisms into sites adjacent to the femoral vessels has reproduced the disease in rabbits. A similar result is obtained by embedding segments of diseased human arteries alongside the femoral vessels (Horton and Dorsey). A surgeon who pricked his finger on a spicule of bone when amputating a leg for Buerger's disease subsequently developed characteristic lesions in the digital arteries of the injured hand. It has been suggested that the disease may be an aftermath of typhus; patients with Buerger's disease show skin hypersensitiveness to rickettsiae. It seems reasonable to suppose that under favorable conditions (age, sex and race) more than one factor might cause acute inflammation of the vessel walls. Not enough stress is laid upon the sex incidence. It is very rare indeed for a disease to be practically confined to one sex. This selectivity must have a bearing on the problem of causation, but so far its real meaning is completely obscure. The excessive use of tobacco, especially cigarettes (sometimes 60 a day), appears to sensitize the walls of the vessels. Sulzberger, by means of skin tests, has shown that these patients are allergic to tobacco proteins, although not to nicotine itself. Allergy is well recognized as one cause of acute inflammatory changes. If a patient has stopped smoking and presents a clean granulating ulcer, resumption of smoking may change the healthy pink granulations into a necrotic gangrenous slough, sometimes overnight, probably owing to vasospasm.

The *lesions* are remarkable for the fact that the acute lesions are of little immediate clinical significance, whereas the late results of these lesions are all important. In this respect the lesion resembles syphilitic disease of the arteries. The *acute lesion* consist of an acute arteritis and periarteritis and acute phlebitis and periphlebitis. The involvement of

both arteries and veins is indicated by the name angiitis. The walls of the vessels are invaded by polymorphonuclear leucocytes, and thrombosis occurs with occlusion of the lumen. Giant cells are often present in the thrombus. Only a segment of the vessel is involved, but this segment may be short or long. The pathologist seldom gets an opportunity to study these acute lesions unless a superficial inflamed vein (migrating phlebitis) is excised.

The *chronic lesions*, so familiar to the pathologist, are seen when the leg is amputated for gangrene months or years later. The artery and vein are bound together by fibrous adhesions (Fig. 365), and the nerve is involved in the same fibrous mass. The lumen of the vessel is occluded by the thrombus, now organized into fibrous tissue, which may be mistaken by the inexperienced for the thickened intima of endarteritis obliterans, a very different condition, although producing similar results. New vascular channels lined by endothelium are formed in the fibrous tissue. The internal and external elastic lamina of the artery are frequently much thickened. There is no calcification as seen in the roentgenogram, a valuable point in differentiating the condition from occlusion due to arteriosclerosis.

Fig. 365.—Thrombo-angiitis obliterans. *Artery and vein are bound together.* × 10.

The *symptoms* are negligible in the *acute* stage with the exception of migrating phlebitis, which is present in about 40 per cent of cases. This is signalized by the appearance of localized red, tender, swollen areas along the line of the superficial veins. As one area subsides another appears. This may be the earliest sign of the disease or may appear late. "In its interpretation there probably lies the secret of the etiology of the disease" (Samuels). Migratory phlebitis may occur independently of Buerger's disease, persisting with intermissions over a period of years and affecting veins in different parts of the body. The etiology and pathology of these lesions are still unknown. In the *chronic* stage the clinical picture is characteristic. The patient, often a young Russian Jew, complains of indefinite pain, burning and tingling in the leg and foot, and observes that these parts are pale and cold. No pulse can be felt at the ankle. He is only able to walk a short distance before violent cramp-like pains develop in the legs owing to insufficient blood supply to the muscles, a condition known as intermittent claudication (*claudicare*, to limp). When the foot hangs down it becomes bright red and throbs painfully (erythromelalgia). When the foot is raised it becomes more blanched than

normal. These phenomena are due to disturbance of the vasomotor control. Later in the disease trophic disturbances appear in the form of ulcers and gangrene of the foot. Trauma is an important precipitating cause of the gangrene. The formation of trophic ulcers is often accompanied by excruciating pain, and suicide is not an uncommon termination of this distressing disease.

Nothing can be done for the chronic lesions, but the young patient has the ability to develop a tremendous amount of collateral circulation. The object of treatment is to keep the formation of the collateral circulation ahead of the advancing occlusive process. Most cases of gan-
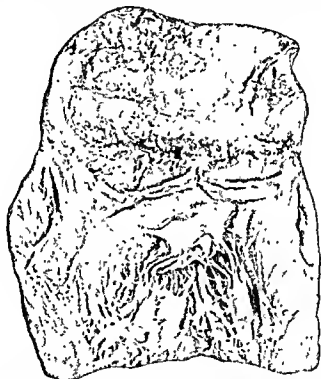
Fig. 366.—Syphilitic aortitis. The surface of the aorta is nodular, wrinkled, and scarred, but there is no ulceration and no calcification.

grene can be prevented by increasing the collateral circulation and avoiding trauma.

Syphilitic Arteritis.—Syphilis of the blood vessels is now such a well-defined entity, and it has until recently been so frequently confused with atheroma and other forms of arterial degeneration, that it merits separate consideration.

Syphilis is primarily a disease of the blood vessels, the spirochetes reaching the vessels in the perivascular lymph spaces. Even in the primary sore the characteristic lesion is the perivascular round-celled infiltration and the thickening of the inner coat. The disease particularly affects, (1) the small arteries, and (2) the aorta.

Syphilitic Arteritis.—Syphilis affects principally the aorta and the

smaller arteries, especially the cerebrals. The spirochetes are carried by the perivascular lymphatics, so that the first change is a periarteritis, characterized by the formation of a ring of lymphocytes and plasma cells in the adventitia and around the vessel. In addition the inner coat shows a regular thickening due to the formation of a young cellular and vascular connective tissue, a condition of endarteritis obliterans. The lumen is narrowed, and thrombosis may occur.

Syphilitic aortitis is the commonest form of vascular syphilis, and is by far the most important cause of aneurism of the aorta. Localized collections of lymphocytes and plasma cells are present in the adventitia and the deeper part of the media, but the whole thickness of the media may be involved. Gummatous necrosis may occur, the most significant effect of which is destruction of the elastic tissue of the media. It is the loss of the elastic tissue which is responsible for the formation of an aneurism. The intima covering the underlying lesions shows a fibrous thickening, so that pale raised plaques appear on the inner surface. These show none of the necrosis, ulceration and calcification which are so characteristic of atheroma. A fine irregular wrinkling like the bark of a tree is an easily recognized feature. (Fig. 366.)

ANEURISM

An aneurism is a localized dilatation of an artery. Almost any artery may be the seat of an aneurism, but the most important are the thoracic aorta and its main branches, the popliteal artery, and the cerebral arteries —both those entering into the circle of Willis and those passing to the basal ganglia.

Causes.—The essential cause is weakening of the arterial wall, especially when associated with a heightened blood pressure. The cause of the weakening may be: (1) in the lumen of the vessel, (2) in the wall of the vessel, and (3) outside the vessel.

Of these far and away the most important is the second. As regards the first, an embolus, particularly if it is infected, will set up an inflammation in the arterial wall, which, through weakening the wall, may give rise to a mycotic aneurism, a complication of bacterial endocarditis not infrequently seen in the cerebral vessels. Examples of the third type of cause are afforded by suppuration in the neighborhood of an artery or still better by the weakening produced by tuberculosis in the wall of an unsupported artery which traverses a tuberculous cavity. Serious pulmonary hemorrhage is often due to the rupture of such an aneurism, which is usually only miliary in size.

Disease of or injury to the vessel wall itself, however, is the cause of those aneurisms which more particularly interest the surgeon. The principal cause of aneurism of the aorta is syphilis which produces great destruction of the middle coat (mesaortitis), particularly of the elastic tissue, thus allowing the wall to stretch and the lumen to dilate. Extensive atheroma in elderly persons may weaken the wall, especially in the abdominal aorta, and allow an aneurism to form.

A stab or bullet wound may give rise to a false aneurism, the walls of which are formed by the surrounding tissues instead of by the vessel wall.

Varieties.—A great variety of aneurisms have been quite unnecessar-

ily described. We may, however, recognize a true and false aneurism, a fusiform and sacculated aneurism, a dissecting aneurism, a traumatic aneurism, and an arterio-venous aneurism.

A *true* aneurism is one in which the sac is formed by the coats of the vessel. When we say coats we really mean the outer coat. The middle coat of a true aneurism is always deficient.

A *false* aneurism is one in which the wall of the sac is constituted by the surrounding tissues. Such an aneurism is often traumatic in origin, and should rather be called a hematoma than an aneurism.

Fig. 367.—Dissecting aneurism of aorta. The middle coat of the aorta is occupied by a dark clot of blood.

A *fusiform* aneurism is a more or less uniform dilatation of the entire lumen of the vessel throughout an appreciable part of its length. It is found in the aorta, and occasionally in some of its large branches.

A *saccular* aneurism consists of a pouching of the vessel at one point. It may communicate with the main lumen by a narrow or a wide opening. It is the usual form of aneurism, and is commonest in the thoracic aorta.

A *dissecting* aneurism is one in which the blood passes up and down in the middle coat of a large artery, nearly always the aorta, separating that coat into two layers (Fig. 367). It is not a true aneurism, because

the vessel is not dilated, but rather a hematoma of the arterial wall. The hemorrhage arises from the vasa vasorum as the result of a degenerative process known as medionecrosis of the aorta. It is possible that in some cases the blood enters the media through an atheromatous ulcer of the intima. With the onset of the medial hemorrhage the patient experiences a sharp pain and a tearing sensation in the chest. Some days later there may be another attack of pain followed rapidly by death due to the blood having ruptured the adventitia and poured into the thoracic or abdominal cavity.

A *traumatic* aneurism, again, is no real aneurism, but rather a hematoma. It is due to laceration of the arterial wall whereby blood

Fig. 368.—Arterio - venous aneurism. The result of a gunshot wound injuring the external iliac artery and vein.

Fig. 369.—Syphilitic aneurism of aorta.

is poured into the tissues, and by its pressure and irritation causes them to become matted together and to form a sac which limits its spread. The laceration may be due to a stab with a sharp instrument or the passage of a fragment of shell, leaving a very minute external wound. In other cases there is no such wound, for the rupture may be due to a sharp fragment of a fractured bone.

An *arterio-venous* aneurism is a condition in which an abnormal

communication between an artery and a vein is established. The cause is similar to that of a traumatic aneurism, namely the simultaneous wounding of an adjacent artery and vein by a bullet, piece of shrapnel, or pointed instrument (Fig. 368). Occasionally the artery alone may be injured, the vein becoming secondarily involved a few days later. Even more rarely an ordinary non-traumatic aneurism may rupture into a vein. The common sites are those places in which a large artery and vein lie side by side, such as the neck, axilla, arm, groin, and thigh.

The distended veins pulsate almost as forcibly as arteries. A marked thrill can be felt and a loud bum heard over the aneurism. In one case to which I listened with a stethoscope the noise was terrific, reminding one of the interior of an engine shop. As the aneurism was in the neck the patient's chief complaint was the continuous noise in his head.

A *congenital arterio-venous fistula* is a direct "shunt" between an artery and a vein without the interposition of capillaries. The blood passes forcibly into the vein, which becomes dilated (arterio-venous varix). The lesion is commonest in the leg, but may occur in the arm or the scalp; in the latter position, it forms a mass of dilated vessels known as a *cirsoid aneurism*. The clinical features are striking and make recognition easy: (1) higher blood pressure and temperature in the affected limb; (2) increased circumference of the limb and the presence of bruits and thrills; (3) cardiac hypertrophy; (4) venous blood is redder on the affected side (pathognomonic); (5) roentgen ray visualization of the fistula after the injection of thorotrast (arteriography).

Fig. 370.—Aneurism eroding vertebrae. The white structure is laminated clot.

Having briefly reviewed the various forms of aneurisms and pseudo-aneurisms, let us now consider somewhat more in detail a true saccular aneurism of such a vessel as the aorta.

An *aortic aneurism* usually commences in the ascending aorta or the arch of the aorta in a vessel whose wall has been weakened by syphilis (Fig. 369). The mouth of the sac, often surrounded by atheromatous plaques, presents a rolled edge like that of an epitheliomatous ulcer. The sac may be of almost any size, and will press upon the adjacent structures. Thus it may grow forward and erode the sternum or ribs with great pain in the chest, or backward and erode the bodies of the vertebrae, sparing the resistant intervertebral discs, and causing great pain

in the back (Fig. 370). It may press on the trachea with difficulty in breathing, on the esophagus with difficulty in swallowing, on the left recurrent laryngeal nerve with hoarseness and aphonia. It may rupture on the surface, or into the trachea, the bronchi, the esophagus, the pericardium, or the pleural cavity.

The lining of the sac is roughened owing to the endothelium giving way. Thrombosis occurs, and layer upon layer of laminated clot is rammed down and becomes incorporated with the wall of the sac. This is an attempt at spontaneous cure, and in the case of small aneurisms it is occasionally successful. The various operative measures employed are attempts to assist this natural process.

The microscopic appearance of the wall of the sac throws much light upon the nature of the condition. The middle coat of the aorta, composed of musculo-elastic tissue, is seen to end abruptly at the edge of the sac, and to take no part in the formation of its wall. The intima is extremely flattened, and here and there the endothelial lining may be shed off. In the later stages it becomes indistinguishably fused with the laminated clot, but there is no evidence of any attempt to organize the clot. The connective tissue of the adventitia is incorporated with the compressed surrounding structures. In the surrounding wall of the aorta there are the characteristic syphilitic perivascular round-cell infiltration in media and adventitia and the medial scars.

It is evident, therefore, that although a true aneurism is defined as one in which the wall of the artery enters into the formation of the sac, there is really not much of the original wall left.

For further information regarding aneurisms the reader is referred to the very exhaustive account by Matas in Keen's surgery, in which an extremely full bibliography is given.

VARICOSE VEINS

A varix or varicose vein is one which is permanently dilated, lengthened, and tortuous. Two chief types may be recognized. In the first, one main superficial vein with its tributaries is affected. In the second, a tangle of distended vessels occurs here and there in the course of a vein.

Sites.—Any vein in the body may become varicose, but there are only three common sites. These are: (1) the veins of the leg and thigh, particularly the internal saphenous (Fig. 372); (2) the veins of the rectum and anus, the condition known as hemorrhoids; and (3) the pampiniform plexus of the spermatic cord, usually on the left side, the condition of varicocele.

Causes.—The predisposing cause, probably in a majority of cases, is a congenital weakness of the walls and valves of the veins. Several members of a family in successive generations may suffer from varix affecting the same vein and even the same segment of vein.

The exciting cause is anything which will bring about increased pressure in the vein. The following factors are important. (1) Central obstruction to the venous return owing to mitral disease, emphysema, or cirrhosis of the liver. (2) The pressure of a tumor, gravid uterus, or chronically loaded rectum. The pressure of tight garters is probably of little importance, although it may aggravate the condition once it is est̲a̲b̲l̲i̲s̲h̲e̲d̲

(3) Prolonged standing, whereby a long column of blood presses continually upon a weakened valve. (4) Straining and violent muscular efforts. The former aggravates the condition of hemorrhoids, the latter is responsible for the frequency of varicose veins in the legs of athletes.

Morbid Anatomy.—The essential lesion is a giving way of the valves, as a result of which all the other troubles follow. The vein becomes dilated and also lengthened; as a result of the latter tortuosity is inevitable (Fig. 371). As a rule the disease is confined to one or more segments, but the vein may be involved in its entire length. The superficial veins of the leg (long and short saphenous) lie just above the deep fascia, and are sup-

Fig. 371.—Varicose veins of leg.   Fig. 372.—Varicose veins of the leg.

ported only by the skin, subcutaneous fat and superficial fascia. It is therefore they which become varicose. The deep veins never become varicose, for they are supported by the overlying muscle and deep fascia and are massaged by contractions of the muscles. The two systems are connected by communicating veins.

A phlebosclerosis develops, similar in many ways to arteriosclerosis. At first there is hypertrophy of the musculo-elastic tissue in the media in response to the increased strain, but later atrophy occurs and replacement by fibrous tissue. The intima also becomes fibrosed and thickened, and in places may greatly narrow the lumen of the vessel. The adventitia

is similarly thickened, and the fibrosis may spread to the perivascular sheath, causing the vein to become adherent to surrounding structures. The walls of the vein may become quite brittle. The thickening is often irregular, so that here and there clusters of pouches may project through the thinner parts of the wall. In such pouches thrombosis will readily occur.

Effects.—The penalty for varicosity has to be paid partly by the veins, partly by the tissues which they drain.

The *veins* may rupture, either externally or into the tissues. The frequency with which this accident occurs in hemorrhoids has earned that condition its name. The bleeding from a varicose vein in the leg may be very profuse and long continued, owing partly to the incompetence of the valves, partly to the sclerosed condition of the vein which interferes with the natural arrest of hemorrhage.

The *effect on the tissues* is even more important. Dickson Wright, whose papers on the treatment of varicose ulcer should be consulted, remarks that in a case of varicose veins of the leg every tissue from the bone marrow to the hair follicles may suffer. As a result of incompetence of the valves of the deep veins and of the communicating veins between the deep and superficial systems, the blood from the deep veins may flow into and down the superficial veins, so that the normal direction of the blood stream is reversed. The blood is picked up in the feet and returned by the superficial veins, and in this way a vicious circle is set up. The blood in varicose veins may have only two-thirds the normal oxygen content, and the carbon dioxide is correspondingly increased. There is a remarkable rise in the pressure in varicose veins in the ankle. When the patient strains this may reach 170 mm. Hg, or 30 mm. higher than the blood pressure in the arteries. The blood from the superficial capillaries is unable to enter the veins against this pressure, so that there is loss of the normal vascular equilibrium and stagnation of fluid in the tissues, which is the root of all the evils which follow. The chief of these are varicose ulcer of the leg, periphlebitis, eczematous skin rashes, and periostitis.

The *varicose ulcer* is a gravitational ulcer, and is a price which man has to pay for the assumption of the erect posture. The skin becomes so sodden that a condition of chronic eczema develops, and the devitalized epithelium is liable to be abraded and ulcerated as the result of a trifling injury. Hemorrhage from a vein in the floor of the ulcer is of frequent occurrence. The ulcer never appears below the line of pressure of the boots or shoes, and the upper limit of the area liable to be affected is the junction between upper and middle third of the leg. The ulcer is extremely indolent, and is a source of the gravest disability in the working classes. When the effect of gravitation is overcome by strapping the ulcerated area and the leg with adhesive plaster of an elastic type, the results are often miraculous (Dickson Wright). *Periphlebitis* is very common, and often forms the starting point of an ulcer. Phlebitis may occur, but, contrary to the usual teaching, it is comparatively rare, else spontaneous cure of the condition would be more common, for the object of the injection treatment of varicose veins is to produce obliteration of the vessel by thrombosis. It is seldom that blood flow in the veins becomes inter-

rupted spontaneously. Owing to loss of the normal vascular equilibrium there is a great collection of fluid in the tissues, so that the part becomes extremely swollen. The skin of the lower part of the leg acquires a mahogany-brown color, owing to the deposit of pigment consequent upon the escape and disintegration of red blood cells. The hair follicles atrophy, so that the lower part of the leg is comparatively hairless. *Periostitis* of the fibula develops as a result of malnutrition of the part.

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THE SPLEEN

In order to understand the surgical pathology of the spleen, it is necessary briefly to consider the part which the spleen plays in the animal economy, its relation to certain other organs, and the effects produced by its removal. Text-books of surgery usually content themselves with a consideration of such conditions as injury, abscess, and tumors of the spleen—well recognized processes which may manifest themselves in the spleen. In addition to these, however, there is an obscure group of conditions in which the spleen appears to be reacting in divers ways to a chronic and long-continued irritant, and with these also the surgeon now finds himself called upon to deal.

Structure.—It is difficult to get a proper idea of the structure of the spleen from sections of ordinary fixed tissue, because there is so much contraction and shrinkage when the organ is removed from the body. The best conception is obtained by the method employed by Robinson, *i. e.,* the study by means of the stereoscopic binocular microscope of thick sections of spleens which have been distended by injection of the vascular system. Gaining in this manner a three-dimensional view, he describes the pulp as "a vast delicate network of star-like cells having irregular protoplasmic processes running in all directions, uniting one cell with the other and forming attachments to the supporting framework." These star-like cells are the reticulo-endothelial cells. The spleen is a reticulo-endothelial organ rather than a lymphoid structure, for the amount of lymphoid tissue is small, and there are no lymphatics. In man the bulk of the reticulo-endothelial system is centered in the spleen, which should therefore be regarded as a vast reticulo-endothelial sponge with a supporting framework of trabeculae and reticulum, and a certain amount of lymphoid tissue superadded, an apparatus admirably designed to detain and alter the blood which is filtered through it. The pathological conditions from which it suffers may affect either the reticulo-endothelial or the lymphoid structures.

The Effects of Splenectomy.—Both in man and in the laboratory animals certain constant effects may be observed after removal of the spleen. The red cells of the blood are diminished in number, but seldom below 3,000,000, and the anemia disappears by the end of two months. A leucocytosis, due mainly to an increase in the number of the polymorphonuclears, persists for about four months. A rise to over 30,000 occurs shortly after the operation, but in a few days' time it drops to 20,000.

In animals the fragility of the red cells is found to be decreased, that is to say they are more than usually resistant to the action of hypotonic salt solution. Hemolytic substances produce jaundice less readily than in the normal animal, and it is of interest to note that in pernicious

anemia in man the urobilin in the urine, a sure index of hemolytic activity, is diminished after removal of the spleen. It would appear, therefore, that in conditions of hyperactivity of the spleen the organ sensitizes the red cells in some way, sets, as it were, its mark upon them, so that when they arrive at the liver they find in it a premature grave. In animals such as rats there is great diminution in resistance to infectious diseases such as rat plague, and although this has not yet been confirmed in man the possibility must be borne in mind.

The cells of the remaining portions of the reticulo-endothelial system undergo proliferation.

Much of the benefit of splenectomy in the several varieties of splenic anemia is probably due, not so much to the removal of injurious substances produced by the spleen, as to the liver being relieved of a large amount of work, it has previously had to deal with the blood from the spleen which forms 25 per cent of the total amount of portal blood passing through the liver. With the enormous spleens found in disease this amount must be greatly increased. Splenectomy, therefore, will relieve the liver of much of its burden, allowing it to catch up with its work, and preventing or ameliorating the symptoms of liver inadequacy which, sooner or later, are apt to develop.

INJURIES TO THE SPLEEN

The normal spleen may be ruptured as the result of severe injury such as automobile accidents. A pathologically enlarged spleen (due to malaria, etc.) may be ruptured by a comparatively minor injury, the so-called spontaneous rupture, which in rare cases may occur even when the spleen is apparently normal. In China, where malarial splenomegaly is so common, an ingenious method of assassination is to cause rupture of the spleen in this way. The bleeding from the torn organ is usually very severe, and the patient dies in a few hours from internal hemorrhage. In other cases, several of which have come to my notice, there may be a curious latent interval of "symptomatic silence" of several days, even a week or more, at the end of which time symptoms of severe hemorrhage suddenly manifest themselves. It seems probable that in these cases the splenic pulp is torn, but the capsule remains intact and prevents the escape of blood, only to give way later with resulting copious hemorrhage. Even when there is primary rupture of the capsule, the contraction of the muscular framework of the organ and the shock attendant on the injury may prevent severe hemorrhage, but after several hours the blood pressure rises again and reactionary hemorrhage begins.

ACUTE SPLENIC TUMOR

In acute infectious fevers, in septicemia, and in acute and subacute endocarditis the spleen is enlarged, and presents the condition known as acute splenic tumor. It is so soft that when incised the splenic pulp can be wiped off like paint, or it may even flow. The cut surface has an opaque, pasty appearance, and is of a dull pinkish-grey color. Microscopic examination shows enormous swelling of the pulp at the expense of the blood-sinuses; the pulp-cells are almost all myelocytes or neu-

txophile leucocytes, evidently produced on the spot in response to the infection. Some of the myelocytes may pass into the blood.

CHRONIC SPLENOMEGALY

A great variety of conditions may cause chronic enlargement of the spleen. Some of these involve the reticulo-endothelial elements and some the lymphoid elements of the organ. The majority of these are of medical rather than surgical interest, but in three of them splenectomy is frequently performed, and these will therefore be considered here. They are Banti's disease, hemolytic jaundice, and purpura haemorrhagica.

Banti's Disease.—This condition, also called splenic anemia, does not possess the sharply-defined limits of a definite entity. It is characterized by progressive enlargement of the spleen, gradually increasing secondary anemia, and in the late stages the development of portal cirrhosis of the liver and ascites. Many cases merge into the picture of cirrhosis of the liver, and it is by no means certain that Banti's disease and Laënnec's cirrhosis are not merely two different aspects of the same condition. The splenomegaly may be the only symptom for a number of years, and it is often a considerable time before the anemia becomes apparent. Several years elapse before signs of liver involvement can be detected; at first the liver is enlarged, but later becomes atrophic. Hematemesis is one of the most important symptoms, and large quantities of blood may be vomited. Bleeding from other mucous membranes may occur. The cause of Banti's disease is unknown.

Morbid Anatomy.—The spleen is greatly enlarged, but when removed it shrinks and collapses owing to a great escape of blood; the cut surface is flabby, and of a greyish-pink translucent appearance. The chief microscopic change is a fibrosis of the Malpighian bodies spreading out from the central artery, and a general fibrosis of the splenic reticulum with thickening of the trabeculae and the capsule.

There is often thrombosis of the splenic vein, the walls of which may be atheromatous and calcified. The vein is usually greatly distended, and there are often huge collateral channels connecting the spleen with the stomach and the diaphragm. The vasa brevia may be represented by great venous channels, which may rupture into the stomach. The danger of this venous enlargement at the time of operation is obvious.

The changes in the liver depend upon the stage of the disease. In the earlier stages it may appear quite normal. Later in the disease it may present the typical appearance of Laënnec's cirrhosis.

The bone marrow is moderately hyperplastic. The lymphatic glands are apparently not involved.

Splenectomy may cure the condition in the early stages, with prevention of the subsequent changes in the liver. The results are uncertain, however, and I have seen a patient die from gastric hemorrhage due to cirrhosis of the liver ten years after splenectomy. If the spleen is very large it should first be reduced in size by means of radiation. The average mortality of the operation is 10 per cent, but in the late stages it may be as high as 25 per cent. The enormously dilated veins in the pedicle of the spleen are an obvious source of danger, and as their walls are rendered

brittle by thrombophlebitis and calcification they are the more easily torn.

Hemolytic Jaundice.—There is no form of splenic enlargement of greater interest to the surgeon than that associated with the condition known as hemolytic jaundice, because nowhere in all surgery are the results of operation more striking and dramatic. A patient who has been deeply jaundiced for years or since birth may acquire a beautiful white skin within 48 hours after removal of the spleen.

Two main forms of the disease are recognized: (1) the congenital or familial type of Minkowski, (2) the acquired type described by Hayem and Widal. It is still open to doubt as to whether it is justifiable to consider these as two distinct diseases, but a number of facts have been observed which appear to warrant the assumption.

The first type is twice as common as the second. The term familial describes this type better than does congenital, for in a number of cases the disease may develop after birth, but it almost always runs through two or more generations.

Clinical Features.—The symptoms of the two forms are very similar. These are: (1) acholuric jaundice, (2) enlargement of the spleen, and (3) anemia. Undue fragility of the red blood cells is a constant feature. Gall stones are present in a large proportion of the cases, and the bile is thick and inspissated. Being acholuric, the *jaundice* differs fundamentally from ordinary obstructive jaundice; there is no bile in the urine although present in abundance in the blood serum, no itching, no bradycardia, and the stools are not clay-colored, but urobilin is present in the urine indicating that there is an increase of hemolytic activity somewhere in the body. In the acquired form acute exacerbations may occur characterized by a rise of temperature, great malaise, a deepening of the jaundice, an increase of the urobilin in the urine, and a temporary increase in the size of the spleen. Such a crisis is undoubtedly due to a sudden increase in hemolytic activity as evidenced by the increase of the urobilin in the urine and the presence in the blood of nucleated red cells and reticulated red cells. Although these crises are supposed to be characteristic of the acquired form, I have seen them in a girl whose sister and brother both suffered from the disease.

The spleen is moderately enlarged, but seldom gives rise to great discomfort. It increases in size during the crises, and may at the same time become tender.

The *anemia* is moderate in degree, the red cells varying from two to three million. It is more severe in the acquired form. The anemia is undoubtedly due to the hemolysis which gives rise to the jaundice. The question is, what is the cause of the hemolysis? Some observers such as Minkowski consider that increased hemolytic activity on the part of the spleen offers a complete explanation. Chauffard, however, pointed out that the most characteristic feature of the blood was an *increased fragility of the red blood cells*, a diminished resistance to hypotonic salt solution. Both he and Widal maintain that the essential feature of the disease is a dystrophy or weakening of the red cells. In one case which I examined the gall stones which were present contained not a trace of cholesterin, suggesting that there may be a poverty of cholesterin

in the protecting envelope of the red blood corpuscles. The improvement which follows removal of the spleen would be quite compatible with such a hypothesis, for a spleen which would do no harm to normal robust red cells would play havoc with such delicate and fragile individuals. In such a case the splenic enlargement would be secondary or spodogenous rather than primary.

Although the two types have so much in common there are certain important points of difference.

The congenital form runs a quieter course. The patient is icteric rather than ill, as Chauffard puts it. Indeed the condition may be so habitual that he consults the doctor about some quite different disease, regarding his jaundice, as Moynihan remarks, with as little interest as the color of his hair. He may be "affected rather than afflicted" by the disease, and may live to an advanced old age. The acquired form, although often quite chronic, is sometimes more eager in its course, it commences as a definite attack of illness, the hemolytic crises are more frequent, and eventually the disease will prove fatal.

The anemia is much more grave in the acquired form, the red cell count in some cases falling as low as 1,000,000, so that the patient is more anemic than jaundiced. Auto-agglutinins are present in the blood in the acquired form, and Widal considers this a proof that the two forms are fundamentally distinct.

Morbid Anatomy.—The spleen is markedly enlarged, weighing on an average about 1000 Gm. Much, indeed the bulk, of this enlargement is due to the blood with which the spleen is filled, and when this blood is squeezed out the organ becomes greatly reduced in size. It is firm, and the cut surface is of a bright red color, something like a beefsteak. The capsule is thickened, and there may be adhesions to the diaphragm.

The *microscopic* picture is striking and characteristic, for the pulp is stuffed with red blood cells, whilst the sinusoids are empty and compressed. The lymph follicles are so widely separated that they may appear to be diminished in number. A large amount of pigment giving the reaction for iron is usually present in the endothelial cells of the sinuses, and these cells may be changed from a flat to an oval shape. The trabeculae and reticulum are not thickened, in striking contrast to what is found in Banti's disease. The media of the arterioles shows a hyaline *thickening.*

Purpura Haemorrhagica.—This form of purpura must be distinguished from the exudative diatheses such as purpura simplex and Henoch's purpura and also from the purpuric hemorrhages which occur as the result of toxic injury to the vessel walls and which may be classed as secondary purpura. It is called primary thrombocytopenic purpura, because the essential lesion is a great reduction in the number of blood platelets or thrombocytes.

Symptoms.—The chief clinical feature is the occurrence of small or large hemorrhages into the skin and from the mucous membranes. The hemorrhage may be spontaneous or traumatic. The bleeding-time is much prolonged, because it depends on the platelets, but the clotting time is normal. Owing to the absence of platelets, there is loss of the normal contraction power of the blood clot in a test-tube. A tourniquet applied

to the arm causes petechiae to appear below the tourniquet, and this forms a useful clinical test.

Lesions.—The essential lesion is the disappearance of the blood platelets. There are no lesions in the tissues. The normal platelet count is about a quarter of a million (200,000 to 250,000 per c.mm.). In purpura haemorrhagica the number is usually below 60,000, and the platelets may disappear entirely. There may be a well-marked secondary anemia, and leucocytosis is present after severe hemorrhages.

Splenectomy.—The surgical interest of the condition depends on the fact that splenectomy may cure the condition. It is important to recognize that there are two forms of the disease, acute and chronic, and it is only the chronic form which is benefited by removal of the spleen. The benefit may only be temporary, and, after a year or two, the hemorrhagic tendency may again manifest itself. The reason for the good effect of splenectomy is quite obscure. Its theoretical basis is the observation that removal of the spleen in a normal animal is followed by a marked rise in the platelet count. This also occurs in man, but unfortunately for the explanation the platelets may fall again to normal in the course of a few months, yet the patient remains well. The removal of the large mass of reticuloendothelial tissue in the spleen is probably connected in some way with the disappearance of the purpura.

TUBERCULOSIS

Healed miliary tubercles are frequently found in the spleen in cases of tuberculosis. Occasionally in general tuberculosis the spleen may be studded with caseous masses of varying size.

Fig. 373.—Sarcoidosis of spleen. The lesions are sharply circumscribed and microscopically are free from caseation.

Occasional cases have been reported of so-called primary tuberculosis of the spleen. In previous editions of this book reference has been made to the specimen shown in Figure 373, a specimen in the University of Manitoba Pathology Museum of a greatly enlarged spleen studded with large masses which were regarded as tuberculous The organ was removed at operation, and the patient remained free from any symptoms of tuberculosis for many years. Reëxamination of the specimen some twenty years later shows lesions which are similar to those of sarcoidosis. It seems probable that most of the cases previously reported as primary tuberculosis of the spleen are examples of sarcoidosis.

ABSCESS

This rare condition is usually secondary to some acute infection such as typhoid fever, acute appendicitis, etc. It may be due to direct extension of infection from a subphrenic abscess.

Enlargement of the spleen, chills, and a marked leucocytosis may suggest the correct diagnosis, which may be confirmed by an exploratory puncture.

Although small abscesses are said to be capable of being absorbed, a large abscess demands splenectomy.

CYSTS

Cysts of the spleen may be: (1) hydatid, (2) dermoid, and (3) simple.

Hydatid cysts are very rare. They may give rise to enormous enlargement of the spleen, which may simulate an ovarian cyst. Suppuration may occur, but frequently the cyst becomes calcified.

Dermoid cysts are of extreme rarity.

Simple cysts may be hemorrhagic or serous. The arteries of the spleen possess no elastic coat and are easily ruptured, with the formation of a hematoma in the spleen pulp. This gives rise to a blood cyst, which is the commonest form of splenic tumor. The cyst is single and may attain a large size. Serous cysts are multiple and small. They seldom give rise to any symptoms.

TUMORS

A *cavernous angioma* may very rarely occur. It appears as a dark, soft mass, which consists of a network of blood spaces. *Secondary carcinoma* is also curiously rare. Carcinomatous cells must constantly be carried to the spleen by the blood stream and arrested there, but conditions for continued growth are evidently unfavorable. In this respect the spleen differs sharply from the lymph nodes. Secondary carcinoma is usually due to primary carcinoma in the breast or lung.

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CHAPTER XXVII

THE LYMPHATIC SYSTEM

To the surgeon the lymphatic system is one of the most important in the body, for it is through the lymphatic vessels that bacterial infection passes from the exterior to the interior of the body, and it is through these same channels that the infection marches from one part to another in sepsis, tuberculosis, and carcinoma, while syphilis, although considered a disease of the blood vessels, reaches those vessels by means of the lymphatics. The lymph nodes, placed here and there in the course of the vessels, and in no sense real glands with an active secretion, constitute one of the most important defense mechanisms in the body, although sometimes they prove woefully inefficient, as in their attempt to destroy carcinoma cells which have been arrested in their interstices. Without these nodes death from general infection would be the universal fate. Friedlander in a series of 133 autopsies in children found tuberculous nodes in the chest in every case, and but for these nodes miliary tuberculosis would have developed in every instance.

The lymphatics of the skin form an abundant anastomotic web. Hudack and McMaster have shown experimentally that the least scratch, even though it does not penetrate the epidermis, causes ready absorption from the abraded surface. Thus every intradermal (not subcutaneous) injection is really an intralymphatic one, every local skin injection soon becomes a general blood injection.

The lymphatics commence as blind diverticula from which first a network and then a series of collecting vessels arises. The system is a closed one, and there is no communication by stomata or otherwise, as used to be thought, between the interior of the vessels and the lymph which bathes the tissues; the lymph has to pass through the unbroken wall of endothelium.

In considering the pathology of the lymph nodes it is helpful to bear in mind that they are made up of two different tissues: (1) a reticuloendothelial network composed of a reticulum of fine fibrils to which are attached a peculiar type of endothelial cells and (2) the lymphoid cells which are contained in the meshes of the reticulum. A pathological process may affect the lymphocytes, the reticular fibers, or the endothelial cells, although usually the two latter react together.

Enlargement of the lymph nodes may be due to a large variety of causes. The enlargement may be due to bacterial infection, the lymph nodes being one of the main mechanisms of defense against such invasion. It may be due to cells of malignant tumors, usually carcinomata, more rarely sarcomata, becoming arrested in the nodes and setting up secondary growths. It may be a manifestation of a general blood condition such as leukemia, in which the nodes may filter out the blood cells or in which the nodes themselves may be the seat of manufacture of such cells. The

enlargement may be due to a general lymphoid hyperplasia in the status lymphaticus. Finally, in many cases the enlargement can be traced to no known cause.

The principal causes of glandular enlargement are: (1) pyogenic infections, (2) tuberculosis, (3) syphilis, (4) carcinoma, (5) Hodgkin's disease, (6) leukemia, (7) pseudoleukemia, (8) lymphosarcoma, and (9) status lymphaticus.

The lymphatic system is commonly affected by the four great diseases—inflammation, tuberculosis, syphilis, and malignant disease, and when the nodes are enlarged these four should first arise to mind, although other less common conditions may also be responsible.

The *preauricular* nodes which drain part of the scalp, the eyelids, and the auricle are often affected by tuberculosis. The *submaxillary* nodes are frequently the seat of tuberculosis and of epithelioma, and as they drain into the deeper cervical nodes the infection may pass into that group. The *submental* nodes are frequently infected by epithelioma, but rarely by tuberculosis. The *sternomastoid* nodes, situated along the posterior border of the sternomastoid muscle, become enlarged in the second stage of syphilis. The *deep cervical* nodes are very often tuberculous, and are often infected from epithelioma of the tongue.

The *supraclavicular* nodes are involved in cancer of the breast; those on the left side may also be involved in cancer of the stomach, infection taking place by way of the thoracic duct. The *lateral* or *retropharyngeal* nodes may become the seat of suppuration or tuberculous caseation, and may give rise to a retropharyngeal abscess. The *axillary* nodes are frequently involved in tuberculosis, cancer of the breast or of the hand, and septic infections of the arm. The *epitrochlear* node becomes enlarged in syphilis. The *femoral* nodes are involved in pyogenic infections of the toes and the sole of the foot. The *superficial inguinal* nodes become enlarged in veneral disease and in epithelioma of the genitals. The *bronchial* and *mesenteric* nodes are very frequently tuberculous.

LYMPHANGITIS

Inflammation of the lymphatic vessels is due to the entrance of bacteria through a wound or abrasion of the skin which may be so minute as to escape detection. Some of the most serious forms of lymphangitis are due to puneture of a finger at an operation or an autopsy on a septic case. The streptococcus is the usual offending organism.

The inflammation commences in the lymphatic reticulum of the skin, and may spread throughout that reticulum, a spread accompanied by the phenomena of erysipelas, or it may pass rapidly up the collecting vessels to the nearest lymph nodes, which become swollen, tender, and painful, and in some cases may suppurate. In a superficial infection of the inflamed lymphatics are seen as wavy, red lines passing up the limb, but if it is deep these lines need not be looked for, although the part will be swollen and will pit on pressure.

As a rule the inflammation ends in resolution, although suppuration at the site of infection is common. Occasionally a severe infection, arrested at the group of nodes into which the lymphatics empty, may set up abscess formation. Should the bacteria pass the line of defense

furnished by the nodes a general infection will ensue, with pyrexia, chills, delirium, and, it may be, death.

The changes in the vessels depend on the intensity of the inflammation. In the milder forms the endothelial cells are merely swollen, but as the inflammation becomes more severe the cells are desquamated into the lumen, and clotting of the lymph occurs. Should suppuration supervene the lymphatics become distended with pus, and present the beaded appearance of a rosary. The surrounding tissues are congested, edematous, and infiltrated with leucocytes.

If the inflammation is at all severe the sequel may be connective tissue formation with lymphatic obstruction and the production of a brawny edema. If the obstruction is at all extensive it may give rise to a condition of elephantiasis in one of its various forms.

LYMPHATIC OBSTRUCTION

Obstruction of the lymphatic vessels may be due to a series of causes which may be divided into external and internal.

Of the more important *external* causes may be mentioned pressure by a neoplasm or a mass of carcinomatous nodes, pressure due to cicatricial contraction, ligature of a set of lymphatic vessels or extirpation of the corresponding group of nodes. A marked example of lymphatic obstruction is sometimes seen in the brawny induration of the arm caused by carcinoma of the breast with involvement of the axillary nodes.

Internal obstruction may be caused by the presence of tuberculosis or carcinomatous material in the lumen of the lymphatics. The most serious of all the causes of lymphatic obstruction is the occlusion due to Filaria bancrofti, the adult form of a nematode worm of which the larval form, the Filaria sanguinis hominis nocturna, is found in the blood in enormous numbers during the hours of sleep. It is not so much the mere presence of the worm that does the damage; it is rather the lymphangitis with subsequent fibrosis and stricture which is the causal agent.

Fig. 374.—Non-parasitic elephantiasis of many years' duration.

The effects of lymphatic obstruction depend upon the site and the extent of the occlusion. The familiar "peau d'orange" or "pig-skin" seen in many cases of superficial breast carcinoma is due, as Sampson Handley has shown, to obstruction of the lymphatics of the skin. Obstruction

of the main lymphatic vessels of a limb may give rise, as has already been mentioned, to a brawny edema of the whole limb. If the vessels of the thorax, especially the thoracic duct, be involved they may rupture and lead to a chylothorax. In the case of the abdominal vessels a chylous ascites will result. The lymph may be poured into the tunica vaginalis or into the loose tissues of the scrotum, with a resulting scrotal enlargement which may pass belief. *The most severe forms of elephantiasis, in which the legs of the unhappy sufferer may come to resemble those of a young elephant, are almost always due to filarial obstruction.*

A peculiar form of lymphatic obstruction is that known as *non-parasitic elephantiasis.* It is met with in non-tropical countries, is slow and

Fig. 375. —*Non-parasitic elephantiasis. Perivascular round-cell infiltration and extreme* edema in the tissues of the hand of a girl seventeen years of age.

insidious in onset, and pursues a chronic and painless course. The legs are generally affected, they are white and firm, and not at all tender (Fig. 374). Most of the cases have been in women, usually about the age of puberty. The condition must be distinguished from Milroy's disease, an edema of the limbs of a markedly familial character which is as common in men as in women. In one case of non-parasitic elephantiasis which I had the opportunity of studying, microscopic examination showed that there was a distinct chronic inflammatory element in addition to the edema (Fig. 375). The patient was a girl seventeen years of age who developed a slow painless enlargement of the hand and wrist, which in the course of eighteen months attained such frightful proportions that the hand had to be amputated. At no time was there any impairment

of her general health. The skin and subcutaneous tissue showed an unbelievable degree of swelling and edema, being of a whitish color and having a pale watery appearance. Microscopically the tissue resembled a myxoma, but there were many collections of small round cells, some of them perivascular in distribution, indicating the action of a chronic irritant. Manson, by the way, does not consider that lymph stasis alone can produce tropical elephantiasis, that is to say a true hypertrophy of the subcutaneous tissue; inflammation is always present in addition in the affected area. The subsequent history of this case is worthy of note. The girl returned four months later with a similar condition in the other arm. As the result of a Kondoleon operation the arm returned to normal size in the course of a month. Six months later the left foot and leg became swollen. A Kondoleon operation produced a similar but even more dramatic result, the swelling melting away in the course of three or four days.

For further information concerning the various forms of lymphatic obstruction, especially those due to the filaria, the very full account by Gerrish in Keen's Surgery should be consulted.

DILATATION OF THE LYMPHATICS

Dilatation of the lymphatics may occur apart from obstruction. This in many cases appears to be a true tumor formation, a lymphangioma, in which there is a formation of new vessels which may be greatly dilated, with the formation of a localized mass. The pathology of lymphangiomas is discussed in Chapter VIII.

The lymphatic dilatation may give rise to great swelling of the part affected. A common form of enlargement of the tongue, macroglossia, is of this nature. So also is macrocheilia, in which the lip is greatly swollen. These conditions are congenital in origin.

A *cystic lymphangioma* is a congenital condition in which the lymph vessels of the tumor undergo cystic dilatation. The resultant mass, which is situated beneath the deep fascia, may vary from the size of a fist to that of a child's head, and may project through the fascia under the skin as a thin-walled almost translucent tumor. The condition may persist for a number of years, and may then undergo spontaneous retrogression. This change is usually due to a series of attacks of inflammation which are liable to occur at intervals, and in which the mass becomes red and inflamed with elevation of temperature. Such a condition may be mistaken for an abscess, and on occasion it has been incised, with somewhat disastrous consequences. True suppuration is very rare, but may occasionally occur. The condition is known clinically as a *cystic hygroma*. The most common site is in the anterior triangle of the neck or under the sternomastoid. It may also occur in the axilla. If the swelling is punctured with a fine needle a clear serous fluid is obtained.

LYMPHADENITIS

The lymph nodes being one of the main lines of defense against infection from without, it is but natural that they should frequently be the seat of inflammation, which itself is nothing but a complex defense mechanism. All degrees of inflammation may be encountered depending

upon the virulence of the infecting bacteria. Two main forms may be recognized, the acute and the chronic.

Acute Lymphadenitis.—This is usually due to infection of the skin or the mucous membranes. The nodes become swollen, painful and tender, and, owing to the periadenitis which is present in all the severer forms, they are matted together. Sometimes it is possible to trace the course of the infection from the primary focus along the red lines of the inflamed lymphatics. Often, however, the infection appears to pass directly from the initial lesion to the nodes, leaving the intervening areas unaffected.

Acute though the inflammation may be, it usually ends in complete resolution. Should the infection be very virulent, and especially if it be due to streptococci, suppuration may occur with abscess formation both in the gland and in the periglandular tissue, with subsequent sloughing of the cellular tissue and of the skin. In these cases the general symptoms will be very marked.

Gross Appearance.—The nodes are soft and hyperemic. On section the color varies from grey to pink, and a milky juice can be scraped from the surface. Opaque areas of necrosis may be discernible, more especially in typhoid and diphtheria.

Microscopic Appearance.—Under the microscope the principal change is a great proliferation of the lymphocytes, as evidenced by the presence of numerous mitotic figures in the germinal centers. In typhoid fever, as Mallory was the first to demonstrate, there is a remarkable proliferation of the endothelial cells, which may completely fill up the sinuses. It is to this cellular hyperplasia, whether lymphatic or endothelial, that the enlargement of the node is mainly due. Hyperemia is usually marked. As the inflammation becomes more severe fibrin is deposited in the lymph sinuses. This is naturally most marked in pneumonia and diphtheria, diseases in which fibrin formation plays so prominent a part. If the inflammation increases in intensity areas of necrosis may appear, due in part to the cutting off of the blood supply by thrombosis and the pressure produced by the cellular proliferation. Suppuration will be accompanied by the appearance of polymorphonuclear leucocytes which crowd the lymph sinuses.

The *occipital* and *superficial cervical* nodes are often infected from pediculosis or wounds of the scalp and the auricle. The *deep cervical* nodes are infected from the teeth and mouth, and when suppuration occurs the pus may spread for some distance beneath the deep fascia. The *lateral pharyngeal* nodes, infected from the pharynx, may suppurate and give rise to a retropharyngeal abscess. The *axillary* nodes are usually infected from superficial wounds or abrasions of the hand, but rarely from septic foci in the deeper structures such as the bones. The *inguinal* nodes are infected from wounds of the leg and foot, boils on the buttocks, eczema of the scrotum, or sores on the genitals in the pyogenic veneral diseases, gonorrhea and chancroid.

Chronic Lymphadenitis.—By far the most frequent cause of chronic enlargement of the lymph nodes is tuberculosis. Apart from tuberculosis and syphilis, however, there may be a simple chronic lymphadenitis due either to the presence in the node of staphylococci or streptococci of a low grade of virulence, or to the irritation produced by foreign particles

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such as dust or carbon. Over 90 per cent of these chronically inflamed nodes occur in the neck, affording striking testimony to the important part which infection of the mouth, tonsils, and teeth plays in the causation of the condition. The inguinal nodes may be enlarged in cases of chronic ulceration of the leg. The axillary nodes are frequently involved in chronic mastitis.

The condition may follow on an attack of acute lymphadenitis. In such a case the glandular enlargement may be due to a reparative fibrosis which renders a return to the former size impossible, or it may be due to the infecting organisms, albeit in a state of diminished virulence, making of the node an abiding home.

Much more frequently, however, the exciting cause must be looked for in some focus of infection in the neighborhood, a focus the removal of which is attended by the disappearance of the glandular enlargement.

Fig. 376.—Sinus catarrh in lymph node. × 150.

The most common of these infections are those of the teeth and tonsils. I have seen a case of persistent enlargement of the cervical nodes in a boy, in which the possibilities of tuberculosis and Hodgkin's disease were considered, but which proved eventually to be merely due to a seemingly inoffensive chronic pharyngitis.

The lymph nodes are enlarged and firm. The general architecture is as a rule fairly well preserved, but there is a hyperplasia of the reticulo-endothelial cells which is sometimes so great as almost to replace the lymphoid tissue, and to convert the node into a reticulo-endothelial structure. In many of my cases, though not in all, the germinal centers have shared in this hyperplasia, with compression and narrowing of the surrounding ring of lymphocytes. Such a picture lends no support to the idea that these centers are made up of lymphoblasts, parent cells of

the lymphocytes. The sinuses, both medullary and peripheral, are often widely dilated and filled with endothelial cells, a condition to which the name sinus catarrh is often applied (Fig. 376). It would be better, however, to refer to the whole process as a reticulo-endothelial hyperplasia. The lymphocytes seem to play no part in producing the enlargement of the nodes.

TUBERCULOUS LYMPHADENITIS

Tuberculosis of the lymph nodes is characteristically a disease of childhood, although it may occasionally occur in adults. In children under one year of age the disease usually runs an acute course, but with every succeeding year of life an increasing resistance is established. The nodes most commonly involved are the cervical (Fig. 377), the bronchial, and the mesenteric.
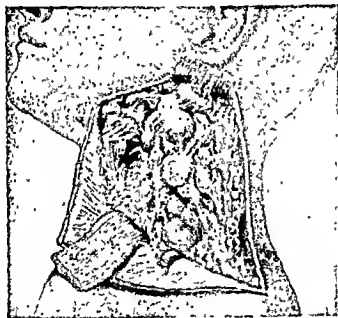
Fig. 377.—Extensive tuberculous involvement of the submastoid, submaxillary, and descending chains. *(Dowd.)*

The bacilli may be carried to the nodes in two ways: (1) by the lymph stream, (2) by the blood stream. The distinction is one of practical importance. Lymph spread is by far the more common, and occurs in about 90 per cent of the cases; the primary focus is in the tonsil, nasopharyngeal adenoids, or carious teeth. A clinical distinction of the two groups is possible, because with a blood infection multiple scattered nodes are attacked, whereas with a lymph infection the disease remains for a long time confined to one or two adjacent nodes. Whatever be thought of operative interference in the lymph spread cases, it is definitely contraindicated in those due to blood spread. In the lymph infections caseation commences at the periphery of the node, since the lymph stream reaches the node at that point. In the blood infections it begins

at the center, because the main blood vessel passes to the center of the node before it breaks up.

Herring has shown that colored solutions when injected into the tissues are absorbed by the blood vessels, not by the lymphatics. Insoluble particles, on the other hand, are taken up by phagocytic cells and carried by them into the lymphatics. "The history of the tubercle bacillus in its early stages in the body is identical with that of solid particles such as Indian ink or carmine. A normal physiological process is made use of for the absorption and arrest of the bacillus. The bacillus is carried into the lymphatics by phagocytic cells, and is deposited in the lymphoid tissue of the first lymph gland arrived at. Some of the bacilli appear to be destroyed in the process, others retain their vitality, multiply in the lymphoid tissue, and give rise to a tuberculous focus in the lymph gland. The toxins produced by the action of the bacilli in a lymph gland mix with the lymph stream and set up an intense lymphocytosis in the other glands through which the lymph passes. The toxin precedes the bacilli and renders the glands less pervious to them by narrowing the lymph sinuses and filling them with lymphocytes." (Herring and Macnaughton.)

Etiology.—The bacilli may be either of the human or the bovine type. The proportion appears to vary considerably in different places. Mitchell found that the bovine bacillus was responsible in 88 per cent of the cases of tuberculous cervical nodes in children in Edinburgh, a most remarkable and alarming figure. On examining the Edinburgh milk supply he discovered that 20 per cent of the samples contained tubercle bacilli. English observers have obtained much lower figures for bovine infection. In New York, Park found that only 34 per cent of glandular cases were bovine in type; in children under five years of age, however, 54 per cent of the infections were bovine. It is very desirable that investigations should be carried out in different parts of the country in order to determine the local incidence of bovine infection in children; the results would provide valuable information regarding the state of the milk supply and the prevalence of tuberculous infection in cattle.

The bacilli reached the cervical nodes from the mouth, passing through the tonsils en route. It is often stated that the tonsils themselves bear no trace of this passage, just as tubercle bacilli may pass through the wall of the bowel and give rise to glandular tuberculosis without producing a lesion in the intestinal mucosa. Mitchell, however, has shown that tuberculosis of the tonsil is commoner than has been supposed. In 106 cases of tuberculosis of the cervical nodes he found microscopic evidence of tuberculosis of the tonsils in 38 per cent of the cases. Even in persons who are apparently healthy tuberculosis of the tonsils can be demonstrated in a considerable number of cases. From a consideration of various large series of figures we may say that in about 5 per cent of individuals evidence of tuberculous infection will be found in the tonsils.

Septic pockets at the roots of teeth are another common source of infection. Tubercle bacilli may be demonstrated in the decayed root pulps of patients suffering from tuberculous nodes in the neck.

An interesting example of the importance of infected milk in the production of tuberculosis of the cervical nodes was reported in Winnipeg by McEachern. A family changed from pasteurized milk to milk supplied

by a small herd and sold unpasteurized. Two and a half weeks after the change a swelling appeared in the neck of the youngest child, who was four years of age. Within the following ten days two of the other children developed enlarged cervical nodes. In two of the cases the enlarged nodes were removed in the Winnipeg Children's Hospital, and I found that they were typical examples of early tuberculosis. The nodes of the other child broke down and discharged through sinuses. The herd supplying the milk was tested, and 87 per cent of the cows were found to be tuberculous.

Apart, however, from the actual presence of tubercle bacilli in the foci of infection in tonsils or teeth, it is undoubtedly the case that chronic inflammation of these organs opens the path for tuberculous infection to spread to the neighborhood lymph nodes, a powerful argument for attention to mouth hygiene in children. Other conditions which may be regarded as predisposing to tuberculosis, inasmuch as they open up the portals of infection, are adenoids, middle ear disease, and lesions of the scalp such as impetigo.

The mesenteric nodes are infected by bacilli passing through the wall of the bowel, or more rarely from a tuberculous ulcer of the bowel. These bacilli may be contained in tuberculous milk, or in sputum infected from the lungs.

Occasionally the axillary nodes may be infected from a tuberculous lesion in the hand, or those in the groin may be infected from the foot.

Clinical Features.—The affected nodes are firm and discrete in the early stages before periadenitis has occurred, and to the hand they feel like so many potatoes in a sack. The nodes can be readily shelled out. The disease may become arrested at this or almost any subsequent stage. Indeed, with the single exception of the skin, it is doubtful if there is any important tissue affected by tuberculosis in which the outlook is more favorable, provided efficient medical treatment is carried out, than in the case of the lymph nodes.

If the disease progresses further periadenitis leads to matting of the nodes into one nodular mass. Caseation and softening may occur, with the formation of a cold abscess, or a mixed infection may result in a true suppuration. The abscess makes its way to the surface, destroying the intervening muscles and fascia, and finally ruptures upon the skin or into an internal cavity. The sinus leading from the node to the surface is lined by tuberculous granulation tissue, and will usually refuse to heal until that tissue is destroyed. There may be extensive cellulitis with involvement of the skin and the formation of multiple sinuses.

Mesenteric lymphadenitis is a condition which demands separate mention on account of the readiness with which it may be confused with other abdominal conditions, both acute and chronic. Among these conditions may be mentioned an acutely inflamed appendix, a gastric or duodenal ulcer, and a stone passing down the ureter. Indeed, as McFadden remarks, there is hardly an abdominal condition for which laparotomy is commonly performed that may not be simulated by diseased mesenteric nodes. It is in children between the ages of 7 and 11 that the condition is most frequent. The nodes, usually those in the ileo-cecal angle or at the root of the mesentery, are found to be enlarged, succulent, and

remarkably inflamed for a lesion caused by the tubercle bacillus. These are the cases which simulate an attack of acute appendicitis. In the center of the mass of nodes there may be a caseous node or a small abscess. In the terminal or healed stage, one or more calcified nodes are found lying in the mesentery. This stage is usually seen in the adult, and the symptoms simulate those of duodenal ulcer, renal calculus, or chronic appendicitis.

It is difficult to explain how the glandular lesion gives rise to the symptoms. In the acute form there may be pain in the right iliac fossa, vomiting, fever, and a leucocytosis of around 15,000. Some of the symptoms are probably due to spasm of the bowel. The

Fig. 378.—A chain of tuberculous nodes in the neck removed by operation.
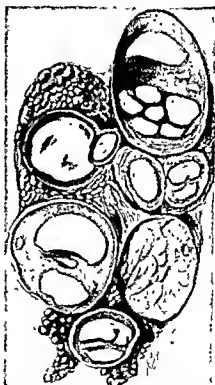
Fig 379.—Tuberculous cervical lymph nodes. The nodes are largely occupied by yellow homogeneous areas of caseation.

leucocytosis is most marked in those cases in which the nodes break down with abscess formation. The acute symptoms are often preceded by a long period of bilious symptoms and periodic attacks of mild pain.

Gross Appearance.—The affected node is enlarged, sometimes to a great size (Fig. 378). On section translucent greyish patches can be seen in the earlier stages, but as the disease advances these become opaque, yellowish, and granular, owing to the occurrence of necrosis and caseation (Fig. 379). In the presence of suppuration a creamy, homogeneous, yellow fluid exudes from the cut surface.

Microscopic Appearance.—Under the microscope the early change is seen to be one of proliferation of the lymphocytes and of the endothelial cells lining the sinuses. When caseation has occurred there are large patches of structureless material staining diffusely with eosin, at the margin of which giant cells may be seen. Tubercle bacilli can be stained in the sections. In long-standing cases there may be a determined effort to wall in the process by the formation of fibrous tissue. Lime salts may be deposited in the caseous material, a very common occurrence in the bronchial nodes. Should healing occur the node is converted into a mass of fibrous and calcareous material.

Reference must here be made to an uncommon but important variety of node tuberculosis, known as *chronic hyperplastic tuberculosis*. It is found most frequently in the intestinal canal, but may also occur in the nodes. It is because of the resemblance of the microscopic picture to that of Hodgkin's disease that the condition specially deserves notice.

The nodes are enlarged and firm, and show no evidence of inflammation. On section they present a grey, translucent appearance, and caseation is absent. Microscopically the brunt of the attack is seen to fall upon the endothelial cells, which proliferate and form small masses, encroaching later upon the rest of the node. There is no increase in the lymphoid tissue. The picture, therefore, is reminiscent of Hodgkin's disease. Caseation hardly ever occurs.

The condition appears to be a very slow and benign form of tuberculosis. Derval has succeeded in producing a similar condition in rabbits by the injection of attenuated tubercle bacilli.

The outcome of tuberculous lymphadenitis, as has already been observed, is usually a favorable one. Indeed in no form of tuberculosis, with the exception of tuberculosis of the skin, is there so little danger to life. At the same time it is by no means uncommon for the disease to spread from the nodes to other and more vital organs. Moreover an apparently quiescent lesion in a node may through rupture into the blood stream give rise at any time either to a general miliary tuberculosis or to a tuberculous meningitis. A tuberculous node must be regarded as but a sleeping volcano.

HODGKIN'S DISEASE

This condition, known also as lymphadenoma, is characterized by progressive anemia with enlargement of the lymph nodes, spleen and liver.

Clinical Features.—The disease is one of early life, and is much commoner among men than women. Its first manifestation is enlargement of the lymph nodes. Several members of one group are involved one after the other, then comes the turn of another group, and so on. The commonest site is the deep cervical nodes, first on one side of the neck and then on the other (Fig. 380). The axillary and inguinal groups are also frequently attacked, less commonly the deep nodes such as the mediastinal and mesenteric. The spleen, meanwhile, is becoming enlarged, and the anemia and other signs of the disease are manifesting themselves.

The nodes are enlarged to a greater extent than in tuberculosis, and are firm, elastic, movable, and quite discrete in the earlier stages,

thus differing from the nodes in tuberculosis. Later, however, some periadenitis may occur, and they become fused together. Great masses may be formed, which may encircle the neck and compress the trachea and esophagus, interfering with breathing and swallowing. Such obstruction, however, is more often due to pressure from similar masses in the mediastinum, the presence of which can be detected most readily by means of X-rays. The nodes show no tendency to softening or suppuration.

Sometimes the deep nodes, mediastinal and mesenteric, are enlarged while the superficial groups escape. Still more rarely the deep glandular enlargement may be unaccompanied by enlargement of the spleen. The

Fig. 380.—Hodgkin's disease. Marked enlargement of the cervical nodes on the right side
Those on the left were enlarged to a lesser degree.

spleen is enlarged in 75 per cent of the cases. In the later stages there may be considerable enlargement of the liver.

The blood as a rule shows no change beyond a secondary anemia, for the proliferating cells remain in the lymph nodes and spleen and do not invade the blood stream. Sometimes there is a sufficient increase in the number of monocytes to be of diagnostic value. In exceptional cases there is a pronounced eosinophilia.

Occasionally there is a peculiar form of pyrexia known as *Pel-Ebstein fever*. The temperature gradually mounts for 3 or 4 days till it reaches about 105°, remains at that level for another 3 days, and descends to normal in a similar period, only to rise again at the end of 10 days or a fortnight. This sequence may be kept up for long periods of time.

Gross Appearance.—The *lymph nodes* are enlarged but remain discrete, not matted together as in tuberculosis until the late stages of the disease when they become fused. They are firm and elastic, and on section have a uniform grey, translucent, moist appearance like that of fish-flesh. Yellow patches of necrosis may break the homogeneous surface. The *spleen* is moderately enlarged, sometimes markedly so. Scattered throughout it are characteristic elastic, homogeneous, yellowish-white, suet-like masses which produce against the red background an appearance like porphyry (Fig. 381). These masses represent the specific Hodgkin tissue. The *liver* may be moderately enlarged. Small opaque pale areas may be scattered over the cut surface. The *bone marrow* may appear red and hyperplastic.

Microscopic Appearance.—This varies with the stage of the disease. The essential lesion appears to be a hyperplasia of the reticulo-endothe-
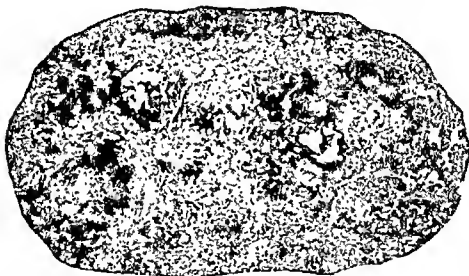
Fig. 381.—Enlarged spleen of Hodgkin's disease showing suet-like areas.

lium, as a result of which the lymphoid structure is gradually replaced (Fig. 382). These cells take the form of large pale cells of epithelioid type, and the picture may bear a close resemblance to the hyperplastic form of tuberculosis. One of the most characteristic features of the lesion is its pleomorphic cytology, in this respect differing from lymphosarcoma. There are many giant cells, both mononuclear and multinuclear, known as lymphadenoma, Dorothy Reed, or Sternberg cells (Fig. 383). Lymphocytes, plasma cells, polymorphonuclears and eosinophils may all be present. Eosinophils are particularly characteristic of Hodgkin's disease, for they are not seen in lymphosarcoma, but they are not invariably present. Necrosis is more frequently seen in the spleen than in the lymph nodes. There is a marked and characteristic increase of reticulum shown by silver staining. This reticulum appears as coarse straight fibrils, and is not a mere condensation of the reticulum normally present. In the late stages fibrosis may be a marked feature (Fig. 384). The picture

which has been described for the lymph nodes is also seen in the spleen, liver, and bone marrow. In the liver the lesions are situated in the portal
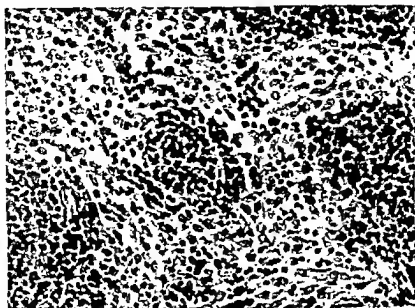
Fig. 382.—Hodgkin's disease, showing endothelial hyperplasia in a lymph node. Some lymphoid cells (dark) still remain. × 250.
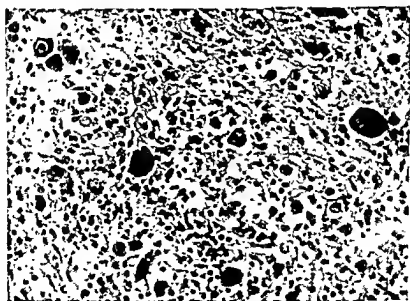
Fig. 383.—Hodgkin's disease, showing the varied cell picture and the large multinucleated giant cells. × 250.

tracts. In the occasional form known as *Hodgkin's sarcoma* there is not the pleomorphism of inflammation but rather the uniform cellular picture

of neoplasia. The cells are large, of uniform size, with abundant cytoplasm and the large prominent nucleolus characteristic of malignancy. Reticulum formation is at a minimum (Fig. 385). In the sarcomatous form of the disease there is much more invasion than in the granulomatous form.

The *course* of the disease is progressively fatal. The enlarged nodes press on vital organs. The cervical and mediastinal masses may cause dyspnea and finally suffocation. Sometimes there is marked invasion of the lung by the mediastinal lesion.

The *response to radiation* differs in the different stages. At the beginning of the disease the glandular masses may melt away in response to X-ray treatment, but when the lesions have become fibrotic there is little or no response.
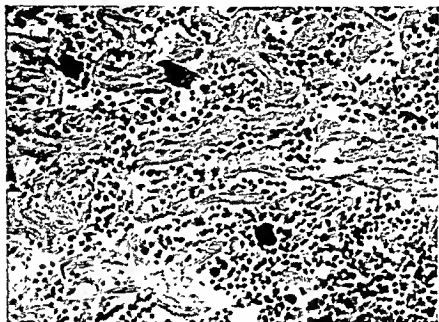
Fig. 384.—Hodgkin's disease showing marked fibrosis. × 250.

Nature and Cause.—The cause of Hodgkin's disease is unknown and even the nature of the condition is uncertain. It has been regarded as: (1) an atypical form of tuberculosis; (2) a specific infective granuloma of unknown origin; (3) a tumor; (4) a transition form between a granuloma and a tumor.

(1) At various times during the past half-century the view has been maintained that Hodgkin's disease is a special form of tuberculosis. Ewing, noting the not infrequent association of the two lesions in lymph nodes, remarks that "tuberculosis follows Hodgkin's disease like a shadow." The arguments against this view seem more formidable than those in favor of it.

(2) The most reasonable view appears to be that the disease is a specific infective granuloma of unknown origin, in which case the name "Hodgkin's granuloma" would be justified. The diversified cytological picture, the necrosis, and the subsequent fibrosis are all in favor of this

idea. Against it may be set the invariably fatal outcome, and the regularity in the distribution of the lesions which is not seen in any of the other infective granulomata. It has been suggested that the infective agent is a filtrable virus on the ground of Gordon's demonstration that injection of a suspension of Hodgkin's lymph nodes into the brain of a rabbit produces a fatal encephalitis, and that stained films of the gland suspensions show minute spherical "elementary bodies" like those of vaccinia virus. Later, however, it was shown that normal human bone marrow contains an agent which will produce encephalitis in the rabbit (Friedemann), and that the Gordon reaction depends on the presence of eosinophils in the diseased tissue (Turner, et al.). Poston and Parsons report finding Brucella melitensis in half the lymph nodes they examined.

(3) The neoplastic theory is the most popular one at the present time. The chief points in its favor are the invariably fatal course and the resemblance to such an undoubtedly malignant condition as lymphosarcoma. The cytological picture is not that of cancer.

(4) The view that Hodgkin's disease occupies a position between the infective granulomata and tumors, as suggested by Symmers and others, offers an escape from an impasse. Without wishing too much to sit on the fence it may be said that the disease partakes of the characters of both of these conditions. The pleomorphism of the microscopic picture suggests an inflammatory lesion, whereas its local spread and its uniformly fatal termination are characteristic of malignancy.

Fig. 385.—Hodgkin's sarcoma, reticulum stain. × 500.

Biopsy Diagnosis.—In actual practice the surgeon relies largely on the pathologist's report on an excised lymph node. In most cases the task is easy, for the histological picture is quite characteristic—a varied picture of hyperplastic reticulo-endothelial cells, mononuclear, and multinucleated giant cells, and eosinophils, together with areas of necrosis and a varying degree of fibrosis. The histological diagnosis may, however, be extremely difficult, and the lesion may be mistaken, on the one hand, for a benign granuloma and on the other for a reticulum-cell sarcoma. The same node examined by three pathologists may be given three different diagnoses. It is well for the surgeon to bear in mind the limitations of the pathologist's technic, and to realize that others besides himself may err.

SARCOIDOSIS: BOECK'S SARCOID

In several respects the condition about to be described is one of remarkable interest. It was first described by Jonathan Hutchison in 1869, but it has masqueraded under such a variety of names that it is

only in recent years that it has come to command general attention. Perhaps the best descriptive name is that of *benign lymphogranuloma*, for clinically the lesions may simulate those of Hodgkin's disease, whilst histologically it may mimic tuberculosis. "Sarcoid" is certainly a misleading name. There is usually an astonishing absence of symptoms, the disease is not fatal, and autopsy reports are correspondingly rare. The condition appears to be particulary common in Scandinavian countries. The etiology is unknown. It has been suggested that the disease is an atypical form of tuberculosis without caseation, but it seems much more probable that it is a chronic granuloma produced by some hitherto undiscovered agent.
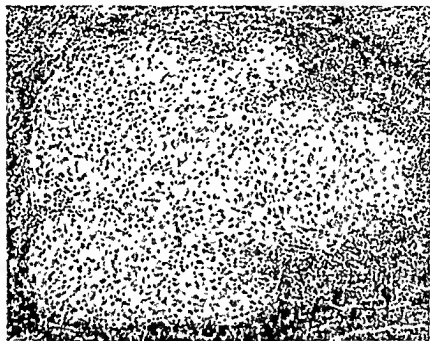
Fig. 386.—Boeck's sarcoid. The circumscribed lesion consists mainly of epithelioid cells with a few lymphocytes but no caseation. × 120.

The diversity of lesions, or rather of organs involved, is remarkable. The chief tissues involved are the skin and lymph nodes, both superficial and deep, but there may be splenomegaly, hepatomegaly, and lesions of the lung, myocardium, pancreas, testis, tonsil, bones of the fingers, parotid and lachrymal glands, and uveal tract of the eye. Symmetrical nodules about the interphalangeal joints may give the fingers an appearance of gnarled branches. To make matters more confusing, lesions may be confined to the skin, lymph nodes, bones, or eye. The disease lasts for months or years, with a tendency to fibrosis and healing. Radiologically the bones, principally the phalanges of fingers and toes, show a peculiar reticulated rarefaction in the early stages; later there are small punched-out areas. There is a remarkable alteration in the plasma proteins, consisting of an unusual increase in the globulin fraction, usually with a pronounced elevation in the total plasma protein. In this respect

the disease resembles multiple myeloma, kala-azar and lymphogranuloma venereum, in all of which elevation of the plasma globulin is a distinctive feature.

The *lesions* are rounded circumscribed masses composed of miliary tubercles (Fig. 386), the components of which are epithelioid cells, macrophages, lymphocytes, giant cells, and occasional eosinophils. The giant cells are larger than those of tuberculosis and contain more nuclei. There is a striking and characteristic absence of caseation. Fibrosis increases with the age of the lesion. Silver stains show a delicate reticulum which is absent, owing to destruction, in tuberculosis.

The lesions are identical with those of *uveoparotid fever* (uveoparotitis) in which there is bilateral painless enlargement of the parotid glands with involvement of the uveal tract. This condition may be regarded as a form of sarcoid due to the same etiological agent.

SYPHILIS OF LYMPH NODES

Syphilis, like tuberculosis, has a special predilection for the lymphatic system. It is true that it is usually regarded as a disease of the blood vessels, but it is through the perivascular lymphatics that the spirochetes reach the vessel walls.

The lymph nodes may be involved in the primary, secondary, or tertiary stage.

In the *primary stage* the nodes nearest the initial lesion become enlarged a few days after the appearance of the primary sore. The inguinal nodes are those usually involved, but in extragenital chancre the epitrochlear, the axillary, or the submaxillary nodes may be enlarged. The node is hard and painless, and is sometimes called a bubo. The swelling is never great, but may persist for many months. Suppuration does not occur unless a secondary infection such as chancroid is superadded. The node is usually swarming with spirochetes. The chief microscopic change is a proliferation of the endothelial cells lining the lymph sinuses. Thickening of the capsule and of the connective tissue septa occurs at a later date.

In the *secondary stage* a general enlargement of the lymph nodes throughout the body, owing to the generalized blood infection, is a constant feature. The epitrochlear and the nodes along the posterior border of the sterno-mastoid should in particular be examined. The histological changes are the same as those of the primary stage, and spirochetes are present in abundance.

In the *tertiary stage* gummata may occasionally be formed in the nodes, but this is a very rare occurrence.

TUMORS OF LYMPH NODES

Our knowledge of tumors of the lymph nodes is by no means as complete as could be desired. There are many difficulties in the way, one of the chief being that lymph nodes react so readily by hyperplasia to the action of a chronic irritant, and such hyperplasia may be indistinguishable from conditions which we regard on other grounds as being true neoplasms. Moreover the relationship of such blood diseases as the leukemias to lymphoid hyperplasia still further adds to the difficulties of the subject.

No attempt will be made here to discuss all the various forms of hyperplasia which may affect the lymph nodes. For such a discussion the reader is referred to the chapter on lymphoma and lymphosarcoma in Ewing's Neoplastic Diseases. From the comparatively simple viewpoint of the surgeon we may say that there are three varieties of malignant disease of the lymph nodes which merit recognition: (1) secondary carcinoma, (2) lymphosarcoma, (3) reticulum-cell sarcoma.

Secondary Carcinoma.—The tumor cells reach the nodes from the primary focus by means of the lymphatics. There are two methods by means of which they may accomplish this, by permeation or by embolism. It appears probable that in the majority of cases the nodes are infected as the result of embolism, but it may well be that in some cases the tumor cells grow along the lymphatics to reach the nodes.

The carcinoma cells first enter the peripheral lymph sinus, gradually permeate the sinuses between the follicles and the cords (Fig. 387), and finally wipe away all trace of normal architecture of the node. At first the node may be movable, if no periadenitis due to associated sepsis is present, but soon the tumor cells invade the capsule and penetrate the surrounding parts, giving rise to dense adhesions. The overlying fascia and skin may become destroyed, and a fungating mass appear on the surface.
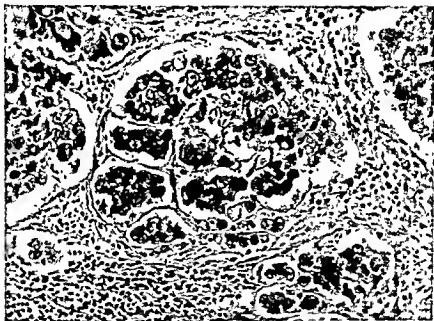
Fig. 387.—Secondary carcinoma in the sinuses of a lymph node. × 175.

The structure of the original tumor is reproduced in the node, be it epithelioma, adenocarcinoma or carcinoma simplex. Indeed not infrequently the secondary growth may be more typical and characteristic than the primary one. It is sometimes difficult to be certain of the nature of a mass in the breast, but the axillary nodes may show a typical carcinomatous structure.

It is not known at how early a date the nodes may become affected, although cancer in some situations gives rise to metastases much sooner than in others. Glandular involvement, for instance, is very much earlier in cancer of the stomach than in epithelioma of the lip. At the same time it must be admitted that a much earlier diagnosis can be made in the latter than in the former. It is never possible to say that in any case of carcinoma the corresponding nodes have not yet become infected. I have seen two cases in which a small epithelioma was removed from the

hand, only to be followed six months later by the development of a metastasis in the axillary nodes.

LYMPHOSARCOMA

It was Kundrat who first separated the condition known as lymphosarcoma from the large and heterogeneous group of the lymphomas. It is characterized by the fact that it arises in one group of lymph nodes or in one collection of lymphoid tissue and spreads to other groups of nodes apparently by way of the lymphatics. Later it may set up true metastases in distant organs. Its other principal characteristic is its tendency to invasion and destruction of the surrounding structures. From what has been said, however, regarding Hodgkin's disease it will be apparent that it does not stand alone in either of these respects. As with the other varieties of lymphoma, we must be prepared to extend or limit the group as fresh evidence arises.

Clinical Features.—The disease is a progressively fatal one, although that is not its chief claim to be regarded as malignant. The symptoms which it produces are on the whole local rather than general, and are mainly due to the pressure produced by the enlarged lymphoid masses in the neck, the mediastinum, and the abdomen. It is remarkable how slight a degree of malignant cachexia may be apparent throughout the course of the illness, in contrast to the cachexia of the later stages of Hodgkin's disease. There is usually a moderate degree of leucocytosis, which in some cases may be sufficiently marked to suggest leukemia. The increase is usually in the polymorphonuclears, but in other cases there is a lymphocytosis, so that it may be impossible to separate the condition from a true lymphatic leukemia. Fever is often a prominent feature, as in Hodgkin's disease. The lymphoid tissue in any part of the body may be involved, so that not only the lymph nodes, but the pharynx, the spleen, the liver, and the gastro-intestinal canal may be the seat of tumor formation. Few tumors are more susceptible to the effect of radiation, and the growth may completely disappear under this treatment. This disappearance, however, may be followed by the death of the patient from asthenia.

For descriptive purposes it is convenient to divide the cases into a number of groups, depending on the principal or primary site of the tumor formation.

Of these groups the commonest is the cervical. The cervical lymph nodes, first on one side, then on the other, become enlarged. As the disease progresses the other superficial lymph nodes, the axillary and the inguinal, follow suit. Closely allied to this group is the pharyngeal form, in which the first lesions are in the tonsil, the sinus laryngis, or the nasopharynx. From these sites the cervical nodes become secondarily infected. These cases are more common than is usually supposed. Gordon New encountered thirty-three in the course of six years at the Mayo Clinic. The primary growth is often quite small, and is frequently overlooked.

The mediastinal form is common and important. In it are seen some of the best examples of infiltration, for the lungs, the bronchi, and other neighboring structures, are extensively invaded. It is usually stated

that lymphosarcoma provides the commonest example of mediastinal tumor. This, however, is by no means certain. Many of these tumors are now known to be thymomas, originating not in the bronchial lymph nodes but in the thymus gland. It has also been shown that it is more

Fig. 388.—Lymphosarcoma. Numerous enlarged mesenteric lymph nodes.

than probable that many supposed lymphosarcomas of the mediastinum are in reality examples of primary carcinoma of the lung with secondary involvement of the lymph nodes. Their infiltrating character is thus more readily understood.

Fig. 389.—Lymphosarcoma. Nodules in large bowel.

The abdominal form constitutes a separate group. Here we must distinguish two varieties. In the one the disease seems to commence in the retroperitoneal or mesenteric lymph nodes (Fig. 388), whilst in the other the starting point appears to be the intestinal lymph tissue, particularly that of the lower part of the ileum. (Fig. 389). It may be difficult to be certain if the glandular form is primary or secondary

to the intestinal lesions. In some cases, however, the intestinal involvement is so great, converting the bowel into a stiff tube, that there is no room for doubt regarding the starting point of the condition. It must be remembered that the hyperplastic form of tuberculosis, involving not only the ileo-cecal region of the bowel but the mesenteric and retroperitoneal lymph nodes may form a stumbling block in the way both of a correct clinical and pathological diagnosis, for the microscopic lesions in the two conditions may be very similar.

The condition of the blood is of interest in view of the resemblance which the condition bears to lymphatic leukemia. A secondary anemia is commonly present. In many cases the leucocyte count is normal. In others the white cells are moderately increased.

Morbid Anatomy.—The enlarged lymph nodes are at first discrete, but presently they become matted together, the tumor cells invade the
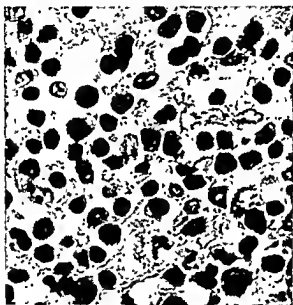
Fig. 390.—Lymphosarcoma. × 1000.

capsule, and the typical local destruction manifests itself. It is only in the primary lesions that this is marked, in, for instance, the pharynx and the mediastinal tissues. I have not observed it in the secondary lesions in the nodes. The cut surface of the nodes is homogeneous, and the appearance is not characteristic. The spleen may be moderately enlarged. Secondary lesions in distant organs, the tumor cells apparently being carried by the blood stream, are found in the liver, kidney, bone marrow, etc. These are usually not visible to the naked eye, and can only be detected by the microscope.

Microscopic Appearance.—The mature lymphocytes are crowded out by much larger hyperchromatic cells with a small amount of basophilic cytoplasm and a round or oval nucleus with a fairly prominent nucleolus; mitoses may be present, but are not easy to recognize. The uniformity of cell type is an outstanding feature in comparison with the

multiplicity of cell forms seen in Hodgkin's disease (Fig. 390). There is no increase in reticulum as shown by silver stains. Those reticulum fibers which are present represent the **original content** of the node, and these are dispersed by the infiltration of neoplastic cells, so that in a given field they appear to be decreased in number (Fig. 391).

In some cases there is a generalized lymph node enlargement rather than a neoplasia commencing in one region and gradually extending and becoming disseminated. In these cases the normal architecture is replaced by mature lymphocytes, and the picture is indistinguishable from that of lymphatic leukemia; only a blood examination can differentiate the two lesions. Such a condition may be called *lymphocytoma*; it may terminate as a lymphatic leukemia.
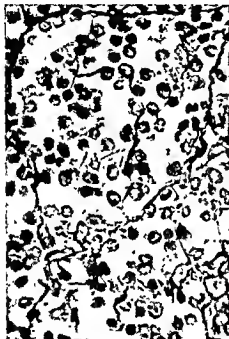
Fig. 391.—Lymphosarcoma. Strands of the original reticulum are widely separated. × 500.

Fig 392.—Reticulum-cell sarcoma. New reticulum surrounding single cells and small groups. × 500.

Giant-follicle lymphoma, also known as *follicular lymphoblastoma* and *Brill-Symmers' disease*, is a variety of lymphoma characterized by an increase both in the size and number of the follicles, many of which may be huge. This appears to be due to proliferation both of lymphoblasts and reticulum cells. The lesions may remain localized for a considerable time. The spleen is involved as well as the lymph nodes. The lesion is of low malignancy and may be present for many years. It has a tendency, however, to terminate as lymphosarcoma or reticulum-cell sarcoma. It is markedly radiosensitive.

Reticulum-cell Sarcoma.— The tumor about to be described is commonly regarded as a form of lymphosarcoma under the name reticulum-cell lymphosarcoma. This is permissible in regard to tumors of

lymph nodes, where the tumor arises from the reticular cells of the node. It may occur, however, in many other situations, including bone, where it forms one variety of bone sarcoma, so that it is better to speak of it as reticulum-cell sarcoma. It is a highly malignant disease, the average duration being less than two years. Although behaving like lymphosarcoma, it may occasionally occur as an isolated lesion, radical removal of which may result in apparent cure. Reticulum-cell sarcoma is a much commoner lesion of lymph nodes than pure lymphosarcoma.

The *microscopic appearance* is characteristic, but this is only true if the material is properly fixed, so as to prevent distortion by shrinkage, and suitably stained. The cytoplasm of the reticulum cell is usually abundant and faintly acidophilic. The nucleus is double the size of that of a lymphocyte, and is commonly infolded, giving it a reniform appearance. Highly characteristic in well-fixed material is the presence of pseudopod-like processes of both cytoplasm and nucleus, indicating ameboid activity in the living cell. The tumor cells may often be seen infiltrating the vein walls and almost closing the lumen. The pathognomonic feature is the distribution of reticulum in silver preparations. In addition to a general increase of the fibers show an intimate relationship to the tumor cells, encircling groups of cells and sending fibrils between and around individual cells (Fig. 392).

Fig. 393.—Endothelioma of lymph node. × 630.

Endothelioma.—In rare cases a lesion of lymph nodes is encountered in which sheets of tumor cells suggest an endothelial origin (Fig. 393). It seems probable that in some of these the cells are derived from the endothelium lining the sinusoids, and the tumor is a primary endothelioma. In such cases the disease tends to become generalized in the lymph nodes. I have seen an occasional rare case which presents this picture, but it is seldom clear cut, and it is difficult to know if one is justified in recognizing the condition as a separate entity. In the great majority of instances the tumor is a secondary carcinoma which mimics an endothelioma. Such lesions are most likely to be found in the cervical nodes.

Difficulties in Diagnosis.—The exact diagnosis of lymphosarcoma is usually made by the microscopic examination of an excised superficial lymph node. In many cases the diagnosis presents no difficulty; the clinical and the microscopic features are in harmony. In other cases there is great difficulty. A leukemic node may exactly simulate a lymphosarcoma, so that in an aleukemic leukemia a mistake may be inevitable. An innocent lymphoma may present an appearance identical with that of a lymphosarcoma. The reticulo-endothelial type may easily be mistaken for a secondary carcinoma. Moreover, it resembles two other conditions, Hodgkin's disease and hyperplastic tuberculosis, in both of which the essential lesion is an endothelial hyperplasia. Single sections

of lymph nodes from lymphosarcoma, round-cell sarcoma, and lymphatic leukemia may all look exactly alike. From all of which it will be seen that the physician should accept with reserve a diagnosis made merely from microscopic examination of an excised lymph node; the whole clinical and radiological picture must be taken into consideration. A number of years ago a mass the size of a pigeon's egg was removed from the groin of a patient who was otherwise in perfect health. From a microscopic section I made a confident diagnosis of lymphosarcoma, but the continued health of the patient for a period of 22 years proved how erroneous was the diagnosis.

Response to Radiation.—The lymphosarcoma group is peculiarly radiosensitive, a fact of great diagnostic value. A large mass of nodes may melt away like snow under the influence of X-rays. The tumor will recur, but can be held in check sometimes for a long period. The lymphocytic type, being more anaplastic, responds much more readily than the reticulo-endothelial type.

STATUS LYMPHATICUS

It is difficult to arrive at the truth regarding the condition known as status lymphaticus, status thymico-lymphaticus, or lymphatism. As long ago as 1614 sudden death was attributed to enlargement of the thymus, and ever since then cases of sudden death from apparently trivial causes have been reported in which the only autopsy finding was general lymphatic and thymus enlargement. Marine in his excellent review of the subject gives the following definition: "Status lymphaticus is a constitutional defect, usually congenital (though it may be acquired), dependent on an inadequacy of some function of the suprarenals, sex glands, and autonomic nervous system, and associated with lowered resistance or increased susceptibility to a great variety of non-specific, physical and chemical agents. Anatomically it is characterized by delayed involution or hyperplasia of the thymus, hypertrophy and hyperplasia of the lymph glands and lymphoid tissue of the various organs, underdevelopment of the chromaffin, gonadal (suprarenal cortex, interstitial cells of testes and ovaries), and cardiovascular systems, and certain peculiarities *of external configuration.*"

On the other hand we must remember that hyperplasia of the lymphoid tissue is very common in children, and that in young persons who die suddenly the thymus may appear to be unduly large owing to the absence of the customary involution of the lymphoid tissue of that organ which occurs as the result of disease. Greenwood and Woods, in a very vigorous paper, the result of an investigation based on rigid statistical methods, remark that status thymico-lymphaticus is a good example of the growth of medical mythology, that a nucleus of truth is·buried beneath a pile of intellectual rubbish, conjecture, bad observations, and rash generalization, and that it is as accurate to attribute the cause of death to "the visitation of God" as to status lymphaticus. Taylor remarks that by some it is viewed as a figment of a disordered mind, an excuse for anesthetists, or a cloak for incompetent pathologists. He adds that one reason for the popularity of the concept is that it restored

the omniscience of the pathologist. "Now he could always find the cause of death, not only in the post-mortem room, but also in the witness box."

Two facts, however, must be admitted. The first is the presence in some persons of hyperplasia of the lymphoid tissue in the throat (pharyngeal and lingual tonsils), the nasopharynx (adenoids), and the intestine, enlargement of the cervical, thoracic, and abdominal lymph nodes, collections of lymphocytes in the liver, kidney, muscles, and especially the thyroid, replacement of the red marrow by lymphoid tissue, and frequent but not invariable enlargement of the thymus. Associated with these changes there will appear diminution of the chromaffin tissue of the adrenals, hypoplasia of the heart and the large arteries with narrowing of the aorta, and a lymphocytosis which may be as high as 60 per cent.

The second undoubted fact is that certain persons have a lowered resistance to drugs, poisons, and other harmful influences. To such persons all general anesthetics are dangerous, and sudden death may follow the administration of cocaine, antiserums, vaccines, and arsphenamine. A historic example is the death of Professor Langerhans' son, who was one of the first to be treated by diphtheria antitoxin. Death may follow the most trivial of causes including extraction of a tooth, tonsillectomy, even the insertion of a hypodermic needle or taking a cold bath.

For a remarkable example of sudden death associated with generalized lymphoid hyperplasia I am indebted to Dr. I. H. Erb, pathologist to the Hospital for Sick Children, Toronto. Some children were playing at the side of the street when a little girl darted across into the side of an automobile. A small boy, aged seven, was heard to shout "I didn't do it," and fell on his face. The girl was unhurt, but the boy, when picked up, was found to be dead. At autopsy there was no evidence of injury, but general lymphoid hyperplasia involving thymus, tonsils, Peyer's patches, mesenteric glands, and Malpighian corpuscles of the spleen. The thymus was very large, weighing 46 grams, and extended from the thyroid gland to 4 inches below the suprasternal notch. The boy appeared to die of fright.

There may not be much justification for attributing sudden death to an enlarged thymus as frequently as is done at coroner's inquests, but on the other hand there can be no room for doubt that the constitutional disturbance known as status lymphaticus is a real entity, and that its most striking clinical feature is a great lowering of resistance. The association of adrenal insufficiency with lymphoid hyperplasia and the condition of lymphatism is of more importance than has commonly been appreciated. Adrenalectomy lowers the resistance of rats to morphine four hundred times, more indeed than any known experimental procedure. This lowering of resistance is accompanied by rapid regeneration of the thymus and the lymphatic tissues. Sudden death is not uncommon in Addison's disease. It would appear then that status lymphaticus may at bottom be due to some deficiency in adrenal function.

The differences of opinion regarding status lymphaticus are well exemplified by two papers, one published in 1931, the other in 1934. The former by Young and Turnbull is a report of the special committee of the Medical Research Council and the Pathological Society of Great

Britain and Ireland, and the conclusion is that the facts elicited "afford no evidence that so-called status thymico-lymphaticus has any existence as a pathological entity." The second paper is by Symmers of Bellevue Hospital, New York, who from his very large experience of autopsies on cases of sudden death is a firm believer in the existence of status lymphaticus. He finds the condition common in suicides and other unstable persons, and often associated with lesions of the ductless glands, e. g., Graves' disease, Addison's disease, and acromegaly. It is a combination of hereditary constitutional anomalies, peculiarities of configuration, persistence or hyperplasia of the thymus, hyperplasia of the lymphoid tissue of the spleen, pharynx and intestine, changes in the distribution of hair, hypoplasia of the vascular system, and failure in development of the genitalia. In childhood the individual is the "angelic child" type, blue or brown-eyed, with transparent skin and soft hair. The adult male is of the feminine type, with delicate skin, graceful body, female distribution of pubic hair, scanty hair on face and body, and small genitalia. The adult female is of delicate build, with very soft, silky skin. It must be realized that although the condition is not uncommon, sudden death is rare. Sudden death in Graves' disease after operation is frequently due to this condition, and Symmers considers that persons with over 40 per cent of lymphocytes in the blood in Graves' disease are bad operation risks.

In addition to the lesions which have already been enumerated, the microscopic picture of the lymphoid tissue calls for special notice, especially in cases of sudden death. The germ follicles often show replacement by whorl-like collections of spindle cells among which are scattered large polyhedral forms. The cytoplasm of both of these cells stains pink with eosin, so that the follicle stands out against the deep blue of the lymphocytes. In children, in whom the danger of sudden death is greatest, the lymphoid tissue in fatal cases shows innumerable necroses of the germ follicles.

Death, which is due to stoppage of the heart, appears to be in the nature of an anaphylactic phenomenon, possibly due to the release of nucleoproteins formed as the result of destruction of the follicles. The hypodermic injection of antitoxins or vaccines may bring on anaphylactic shock in a hypersensitive individual, or substances manufactured as the result of shock from the prick of a needle, sudden immersion in cold water, etc., may act in the same way. Cerebral hemorrhage in young non-syphilitic subjects is probably often due to status lymphaticus, owing to the hypoplastic condition of the thin-walled cerebral arteries. Pressure of the enlarged thymus on the trachea is a factor of no importance.

THE THYMUS

The thymus gland may be regarded as a portion of the lymphatic system. It consists, however, of two entirely different tissues, different in origin, in structure, and probably in function. These tissues are: (1) the epithelial cells, derived from the fourth branchial cleft, which constitute the medulla of the gland where they are collected in the aggregations known as Hassall's corpuscles and are also found in the cortex as the reticular cells, and (2) the lymphoid cells which make up the greater part of the cortex. The thymus is essentially an epithelial organ infiltrated by lymphocytes.

At birth it weighs 13 grams, gradually increases in size till the age of puberty when

it weighs about 35 grams, and from that period onwards undergoes a gradual atrophy. It continues, however, to function actively throughout life.

The thymus is never found in a normal condition in persons who have died from disease, for it responds with great readiness to hostile influences, and the cortex becomes greatly reduced by increased emigration of lymphocytes, so that the entire gland may be only one hundredth of the normal weight. As a result of this shrinkage of the lymphoid tissue there may be a relative increase in the number of the Hassal corpuscles which is more apparent than real. An erroneous idea of the normal size of the thymus is therefore obtained at autopsy, and in cases of sudden death the unaltered thymus may appear to be unduly large. This accidental involution is produced not only by the majority of diseases but also by other influences such as manition, pregnancy, and X-ray treatment.

Hammar of Upsala in a series of studies on the thymus has shown that there may be a true increase in the epithelial cells and the Hassal corpuscles, even though the bulk of the gland is diminished. This increase takes place in response to the introduction of any antigenic toxin into the body, and it can be particularly well demonstrated in the case of diphtheria toxin and snake venom. It would appear that the function of the epithelial cells may possibly be antitoxic in nature.

Thymus Hyperplasia.—Hyperplasia of the thymus is frequently found in Graves' disease, in the so-called thymic death, and in a number of other conditions of less importance, such as Addison's disease, myasthenia, acromegaly, and castration. In Graves' disease there is a great increase of the lymphoid tissue of the cortex which is apparently merely one manifestation of the general lymphoid hyperplasia found throughout the body. The Hassal corpuscles may also show a marked hyperplasia. There is thus a definite increase in both of the thymic tissues, an increase which is also observed when an animal is fed on thyroid gland. The Hassal corpuscles may also show a marked hyperplasia.

Thymic death is a term which includes two quite different conditions. The first is thymic asthma, characterized by inspiratory dyspnœa; it is caused by pressure of the enlarged thymus on the trachea, and death takes place from suffocation. The second is the true thorn thymus, in which there is no difficulty in respiration, and death may occur quite suddenly and unexpectedly in an apoplectiform manner; it may be during sleep, due apparently, to heart failure. From a microscopic study of 37 of these cases in children Hammar came to the conclusion that the thymus was not directly concerned with the cause of death, and that the apparently large size was due to the absence of accidental involution.

Tumors of the Thymus.—The only tumor of any importance is that known as the thymoma, and even it must be considered a rarity. Much confusion exists as to its true nature, and several varieties have been described. Two main types may be distinguished (1) malignant thymoma or lymphosarcoma, and (2) carcinoma.

The malignant thymoma resembles in structure a lymphosarcoma, but careful examination will reveal differences. The cells are larger than those of the typical lymphosarcoma, large pale cells recalling those of Hodgkin's disease may be seen, and occasionally giant cells are present. Although it is commonly thought that the cells are derived from the lymphoid cells of the gland. Ewing and others consider that they originate from the reticulum cells.

The carcinomatous type is composed of masses of pavement or cuboidal epithelium, with concentric layers of cells resembling Hassal's corpuscles. The tumor probably arises from the epithelial elements of the gland.

Both of these tumors are highly malignant. They compress and invade the surrounding structures, and may extend downwards as far as the diaphragm. The bronchial, cervical, and axillary nodes become involved. A thymoma forms one variety of mediastinal tumor. Metastasis to distant organs sometimes occurs.

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CHAPTER XXVIII

THE CRANIUM AND ITS CONTENTS

Before considering the cranium, the brain, and the meninges, a few words may be devoted to the scalp.

THE SCALP

The scalp is subject to the same diseases as the skin in other situations. It presents, however, one or two anatomical peculiarities which have a bearing on the pathological processes to which it is liable. The skin is bound to the epicranial aponeurosis of the occipito-frontalis muscle by dense fibrous tissue in which run the vessels which supply the scalp, and with which the outer coat of these vessels is continuous, so that when cut they are unable to retract. It follows, therefore, that when an artery is divided the bleeding is apt to be very persistent.

The vascular supply of the scalp is extremely abundant, so that it is very rare for a portion, however badly damaged, to die. For this reason the surgery following injuries can be conservative in the extreme, and no portion of the scalp, however hopeless it looks, should be sacrificed.

Very free communications exist between the veins of the scalp and the intracranial venous sinuses by means of the emissary veins which pass inwards through the skull, and which may be the ready means of conveying infection to the interior of the cranium. Every wound of the scalp carries with it possibilities of future mischief unless all bacteria are carefully excluded.

Finally, the connective tissue between the aponeurosis of the occipito-frontalis and the cranium is so loose that it offers no resistance to the spread of blood from a bleeding vessel. A large blood tumor may thus be formed, which is known as a subaponeurotic cephalhematoma. In some cases the blood may be poured out beneath the pericranium, with the formation of a subpericranial cephalhematoma. The latter is naturally bounded by the limits of the bone to which the pericranium is attached, the former is irregular in shape, and may be only limited in size by the attachment of the occipito-frontalis itself. This form of hemorrhage is often due to the use of instruments during delivery.

Of the diseases of more particular interest affecting the scalp may be mentioned epidermoid carcinoma, wens, dermoid cysts, sebaceous adenoma, cirsoid aneurism, and plexiform neuroma.

Epidermoid carcinoma presents the usual picture of a malignant ulcer of the skin. It may invade the skull, and in such cases it may be mistaken for a sarcoma of the skull invading the skin.

Wens are sebaceous cysts of the scalp, with little or no hairy covering, frequently multiple, and usually occurring in the later years of life.

Dermoid cysts, being congenital in nature, are met with in childhood.

They are commonest over the anterior fontanelle and the occipital protuberance.

Adenoma of the sebaceous glands is a rare condition, but apt to be puzzling unless its presence is kept in mind. It forms a solid mass with a very thin covering of skin. One specimen in the University of Manitoba Pathological Museum is as large as a medium-sized potato.

The so-called *turban tumor* of the scalp is a condition in which multiple benign epithelial tumors are grouped together to resemble bunches of grapes or tomatoes. They may be so numerous as to cover the entire scalp giving an appearance like a turban. The condition is also *known as Spiegler's tumor. It seems likely that the tumors are of sweat* gland origin. Microscopically they resemble the cystic adenoid epithelioma of the skin (Brooke's tumor) which occurs in other parts of the body.

A *cirsoid or arterio-venous aneurism* forms a mass like a bag of worms. It is made up of a great number of tortuous, dilated, pulsating vessels, and is in no sense a true aneurism. The patient's chief complaint is of a rushing noise in the head.

A *plexiform neuroma*, affecting the branches of the fifth nerve, occurs as a diffuse soft mass in which separate cords can be made out. Other forms of neurofibromatosis may also be met with in the scalp.

DISEASES OF THE CRANIAL BONES

The chief pathological conditions affecting the cranial bones are the usual four, inflammation, tuberculosis, syphilis, and tumors.

Osteomyelitis.—Osteomyelitis of the cranial bones differs from that seen in other bones in that it is much more frequently secondary to wounds of the scalp, infected fractures, middle ear disease, etc., than primary in origin. This is due to the absence of the vascular epiphyses and metaphyses which are so frequently the seat of infection in the long bones. Thrombophlebitis of the diploic veins is the most important feature of the process, for it may extend far beyond the range of the surgeon's eye, and be responsible for fatal intracranial complications.

The inflammation when derived from the outside affects principally the outer table; when primary in the bone it commences in the diploë and spreads outwards. The sequestrum produced is, therefore, as a rule, quite superficial. A very long time is occupied in its separation, and there is remarkably little new bone formation, so that if there is a large bony defect it remains largely unfilled.

The inflammation may spread to the dura causing a subdural abscess, to the pia-arachnoid causing a septic meningitis, or to the cranial sinuses causing a sinus phlebitis. When an abscess forms between the dura mater and the bone the overlying skin becomes swollen and edematous, the condition known as "Pott's puffy tumor," which will be alluded to again presently. It indicates not only the position of the inflammation, but to some degree its extent.

Osteomyelitis of the frontal bone secondary to frontal sinusitis deserves special mention, as it is one of the most fatal surgical diseases. Many of the most fulminating cases can be traced to swimming. The veins of the mucous membrane of the frontal sinus are continuous with the huge diploic veins of the frontal bone, and these in turn connect the veins

of the scalp with all the blood sinuses. It is evident that infection of the frontal sinus if accompanied by thrombophlebitis of the mucosal veins may be followed by widespread osteomyelitis. Extradural and subdural abscess, meningitis and brain abscess are common complications.

Tuberculosis.—Tuberculous disease is commoner among children and adolescents than among adults. The bones most frequently attacked are the frontal and parietal; much less frequently the temporal and occipital. Two forms of the disease are usually described, the perforating form and the diffuse progressive infiltration. This distinction has broken down, and it is probable, as Valentine St. John puts it, that there is but one form of tuberculosis of the cranial vault, circumscribed in the early stage and diffuse in the later.

The disease commences in the loose tissue of the diploë, through which it spreads, attacking here and there the tables of the skull. Both tables may be attacked at the same point, with the resulting formation of a sequestrum involving the whole thickness of the bone. Or the outer table may be destroyed and a cold abscess formed, which at first lies between the pericranium and the bone, but later perforates the pericranium and comes to occupy the loose tissue of the scalp. Finally, the disease may extend inwards, the inner table is perforated, and the dura exposed. A pachymeningitis is the natural result, but a true tuberculous meningitis is a rare complication, owing perhaps to the thickening of the dura. Moreover it is very unusual for a cold extradural abscess to form in situ, although pus may make its way from the outside of the skull through the opening in both tables, and thus reach the interior of the cranium.

It is sometimes stated that tuberculosis destroys the inner table so much more than the outer that the area of erosion becomes funnel-shaped with the mouth of the funnel looking inwards, but this is not sufficiently constant to be of any diagnostic value. The perforation in the outer table may be single or multiple; as many as 29 perforations have been found in the skull of a child.

Syphilis.—The only important syphilitic manifestation in the cranium is the gumma. A gumma forms a painless, elastic swelling which may be mistaken for a sarcoma, a subperiosteal abscess, or a cold abscess. Although the gumma is painless to the touch, syphilitic ostcitis is usually accompanied by pain, sometimes of a very severe nature, and characteristically worse at night.

Unless infected the separation of the necrosed portion occupies a very long time. Infection, however, is very liable to occur, and necrosis is then much more rapid and extensive, so that a macerated specimen will show the widespread worm-eaten appearance so frequently seen in museums. It is the outer table which is principally affected, although the inner table may be involved to a lesser extent. The mouth of the funnel in this case will be directed outwards. If several gummata are present the necrosed bone presents the appearance of intersecting circles, and large sequestra may be formed which on separating leave correspondingly large defects in the skull.

The lesions of syphilis differ from those of osteomyelitis and tuberculosis in that they are accompanied by a considerable amount of bony

overgrowth. When healing occurs, therefore, a depressed scar is left with definitely raised bony edges.

Tumors.—*Osteoma* of the skull has already been described on page 126.

Sarcoma.—A sarcoma usually arises in the periosteum, but it grows rapidly and may soon penetrate to the interior of the cranium. It forms a soft, diffuse swelling which may be mistaken for a gumma or an abscess. The prognosis could not be worse.

Secondary Tumors.—Metastases in bone, and particularly in the cranium and spine, are peculiarly apt to occur in carcinoma of the thyroid, the breast, the lung, the prostate, and in hypernephroma. The growths may be single or multiple, and frequently lead to errors in diagnosis. A large secondary tumor of the frontal bone is an occasional accompaniment of carcinoma of the thyroid.

A palpable and even visible mass may result from invasion of the skull by a meningioma, with hyperplastic thickening of the bone. In such a case there will be symptoms of an intracranial tumor.

THE CEREBROSPINAL FLUID

Before passing to the subject of hydrocephalus a short review of the methods of production and absorption of the cerebrospinal fluid will be necessary, and a brief reference will be made to the functions of the fluid and its behavior under pathological conditions. An examination of the cerebrospinal fluid is of enormous value in arriving at a correct conception of what is transpiring within the cranial cavity, for the fluid is the sensitive mirror in which is reflected many a tell-tale picture of cerebral disease.

The cerebrospinal fluid is contained in the ventricles of the brain and in the subarachnoid space. In the cranial cavity two spaces may be recognized, the subdural between the dura and the arachnoid, and the subarachnoid between the arachnoid and the pia. It is curious that there is no communication between these two, so that not only an extradural hemorrhage but even a hemorrhage into the subdural space may show no blood in the spinal fluid. Often, however, the arachnoid is torn by the initial injury, so that in a fracture of the skull with middle meningeal hemorrhage the discovery of blood at lumbar puncture may be of great diagnostic importance. The possibility of the blood being due to the puncture must always be kept in mind. The method of differentiating pathological from puncture hemorrhage is given on page 605.

The fluid is secreted in the lateral ventricles and the third ventricle by the choroid plexus, passes along the aqueduct of Sylvius to the fourth ventricle, and escapes thence into the cerebral subarachnoid space through the small openings in the membranous roof of the ventricle— the median foramen of Magendie and the two lateral foramina of Luschka.

The arachnoid clothes the brain much in the same way that a mitt covers the hand; it does not adapt itself closely to the convolutions, nor dip down into the fissures. The pia, on the other hand, may be compared to a closely fitting glove, which adapts itself to every fold and fissure of the organ.

The *subarachnoid space*, which over the upper part of the brain is

of the narrowest dimensions, widens out into cavernous cisterns at the base. It is into these cisterns that the fluid is poured from the fourth ventricle, and it passes forward and upward under the medulla, pons, and midbrain in a manner which will be described more in detail in discussing the production of hydrocephalus. The spinal is continuous with the cerebral subarachnoid space, and passes downwards as far as the third piece of the sacrum. As the spinal cord ends at the lower border of the first lumbar vertebra the cerebrospinal fluid may be withdrawn with safety by means of lumbar puncture from any part of the intervening space. Lying between the posterior surface of the medulla and the cerebellum is a continuation upward of the posterior part of the spinal subarachnoid space, the cerebello-medullary cistern. It is into this large space that a needle is passed in withdrawing fluid by cisternal puncture. The cisterna pontis, in front of the medulla, is continuous with the anterior part of the same space. The cisterna basalis stretches between the temporal poles and is in relation to the important interpeduncular space.

The subarachnoid space sends very important extensions filled with fluid into the substance of the brain. As the cerebral arteries pass into the brain they carry with them a fine, sleeve-like sheath which accompanies the vessel until it becomes a capillary. The wave of fluid resulting from a sudden blow may thus travel deep into the substance of the brain and give rise to those ecchymoses which have already been discussed in relation to concussion. The cerebrospinal fluid may therefore be compared to an expanse of water with rivers, innumerable rivulets, and a few deep lakes.

Absorption takes place into the great venous sinuses through the medium of the arachnoid villi, which are prolongations of the subarachnoid space projecting for the most part into the superior longitudinal sinus, and perhaps also directly from the subarachnoid space into the cerebral capillaries. The greater part of the absorption occurs above the level of the tentorium cerebelli, so that if some form of obstruction should prevent the flow of the fluid from the lower to the upper part of the cranial cavity hydrocephalus will result even though the aqueduct of Sylvius and the foramen of Magendie are both open.

The *pressure* of the cerebrospinal fluid, which is normally about 7 to 9 mm. of mercury or 110 to 130 mm. of normal saline, is always considerably above that of the sagittal sinus. Wegeforth demonstrated this in a striking manner by establishing an experimental communication between the subarachnoid space and the superior sagittal sinus. The opening in the wall of the sinus remained open for four days without hemorrhage occurring into the subarachnoid space. Lowering of the cerebrospinal fluid pressure by lumbar puncture, however, at once led to hemorrhage. The practical application of this observation to such a condition as subarachnoid hemorrhage in the new-born is obvious. Weed and McKibben have shown that the pressure of the cerebrospinal fluid is markedly altered by the intravenous injection of solutions of various concentrations. Strongly hypertonic solutions lowered the cerebrospinal fluid pressure to an extreme degree whilst hypotonic solutions such as distilled water produced a prolonged rise. Cushing and

Foley found that a similar effect could be produced by the ingestion of saline fluids.

Functions.—The function usually assigned to the fluid is a purely mechanical one, and no doubt it plays an important part in shielding the central nervous system from the rude shocks and blows of the outside world. The medulla, the most delicate and vital part of the brain, is surrounded by the cisterna magna and the cisterna pontis, so that the brain may be regarded as supported by a water cushion which serves to protect the more sensitive parts from harmful jarring.

Moreover, the fluid is able to flow from the cranial into the spinal cavity. As the skull is a rigid and inexpansile box this shifting of the fluid is of great value as a safety valve whereby the brain is permitted to expand. Even such acts as coughing or crying at once cause the fluid to flow out of the skull, and in cerebral congestion and edema and in the early stages of cerebral tumor this mechanism saves the brain from injurious pressure.

Important as these functions may be, there can be little doubt that the fluid is above all concerned with the nutrition of the central nervous system and the elimination of waste products. The cerebrospinal fluid bears a remarkable resemblance to Locke's physiological saline solution, which contains sodium chloride and a small quantity of glucose, and this is an ideal medium for nourishing the tissues and removing the products of metabolism. The cerebrospinal fluid, therefore, may be regarded as the lymph of the brain.

Diagnostic Value of Lumbar Puncture.—An examination of the cerebrospinal fluid affords valuable evidence, either positive or negative, in the following conditions: fracture of the skull, cerebral hemorrhage, meningitis whether acute, tuberculous, or syphilitic, cerebral abscess, cerebral tumor, and tumor of the spinal cord.

Fracture of the Skull.—If the fracture is accompanied by hemorrhage, and if the dura and arachnoid have been torn, blood will appear in the spinal fluid. This is most likely to occur in middle meningeal hemorrhage and in fractures of the base of the skull. Only positive evidence is of value. The absence of blood does not indicate the absence of a fracture. Probably the commonest cause of blood in the spinal fluid in cases of fracture of the skull is "contre-coup" laceration of the cerebral cortex with hemorrhage in the subarachnoid space.

Pathological blood must be distinguished from puncture blood. Collecting the fluid in two tubes, and centrifuging the fluid with examination for hemolysis, will usually settle the matter. If the hemorrhage is very recent there may be no hemolysis, as sufficient time has not elapsed for it to be produced. I have seen a case of fracture of the skull, examined within 24 hours of the injury, in which centrifuging removed every trace of blood. The source of the blood was evident, however, for it was so abundant and so constant in its flow that it could not possibly have come from the wounding of the plexus of veins which lies in the anterior wall of the spinal canal.

Cerebral Hemorrhage.—In cerebral hemorrhage there is not likely to be blood in the spinal fluid in the early stages. About 40 per cent of fatal capsular hemorrhages rupture into the lateral ventricle before

death. Pontine hemorrhages almost invariably rupture into the fourth ventricle. Spontaneous intracerebral hemorrhage only very rarely ruptures outward into the subarachnoid space. In the newly-born blood is often present in the spinal fluid owing to tearing of the delicate veins which pass from the cortex to the superior longitudinal sinus, the tear being produced by the strain induced by the molding of the parietal bones.

Meningitis.—The diagnosis of meningitis depends upon spinal fluid examination. In acute meningitis the fluid is under pressure, turbid owing to the presence of pus, a coagulum forms which sticks to the side of the tube, there is marked increase of the protein and an extremely high cell count, and the specific organisms can be found in smear or cultures.

In tuberculous and syphilitic meningitis the fluid is as a rule quite clear, although it may be slightly opalescent, there is a moderate increase in the protein, and a lymphocytosis of from 50 to 100; in the tuberculous variety a fine filmy clot forms, which floats like a cobweb in the center of the fluid, and in which tubercle bacilli can frequently be demonstrated if sufficient
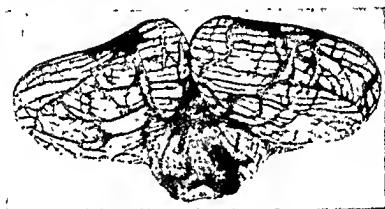
Fig. 394.—Cerebellar pressure cone.

time be taken. In syphilitic meningitis the Wassermann reaction is usually but not invariably positive in the spinal fluid as well as in the blood.

Cerebral Abscess.—In abscess of the brain the condition of the spinal fluid should be helpful, but may be misleading. It will not mislead if it is borne in mind that a cerebral abscess may be associated with a perfectly normal fluid. Indeed it is the very negative character of the fluid which is of differential value in distinguishing abscess from meningitis, the condition with which it is most apt to be confused. If the abscess approaches the surface, polymorphonuclears in moderate numbers may appear in the fluid, due apparently to scepage of irritating material into the subarachnoid space. Rupture of the abscess is more likely to take place into a ventricle than into the subarachnoid space; in either case the clinical picture is that of a fulminating meningitis.

Cerebral Tumor.—The only reason why I have included cerebral tumor in the list of conditions in which lumbar puncture is of diagnostic value is in order to condemn the procedure. Lumbar puncture should never be done in a suspected case of cerebral tumor, except it be for the purpose of ruling out a syphilitic infection. The operation is not only

dangerous but valueless. The high pressure under which the fluid spurts out is, it is true, an indication of a heightened intracranial pressure; but if the clinician is unable to diagnose such a heightening of pressure without laboratory assistance he would be well advised not to undertake the care of a brain case.

The danger is greatest in those cases where the tumor is situated in the posterior cranial fossa below the level of the tentorium cerebelli. The accident is usually due to the medulla being forced, as a result of the high pressure above and the lowered pressure beneath, like a plug into the foramen magnum with fatal pressure on the vital centers. To be more accurate, it is the cerebellar tonsils which are forced into the opening, and which may in turn press upon the medulla. The groove produced by the pressure may be seen in fatal cases on the side of the cerebellar tonsils (Fig. 394). In supratentorial tumors there is a downward thrust of the whole brain stem with plugging of the incisura tentorii by the upper midbrain and the hippocampal unci. In some cases no evidence of plugging or compression of vital centers can be observed. Here the probable explanation is that the sudden decrease in external pressure is followed by dilatation of the cerebral vessels and acute medullary edema. In a vascular glioma with thin-walled vessels a sudden fall in pressure may be followed by a fatal hemorrhage.

If the clinician is determined to do a lumbar puncture, not more than 2 c.c. of fluid should be withdrawn, and if the fluid spurts out the operator should at once pluck out the needle. Needless to say, the patient should be in the recumbent posture. The use of a manometer is a valuable safeguard. Not only does it indicate the increased pressure before the fluid is withdrawn, but it enables the withdrawal to be made very slowly.

Tumor of the Spinal Cord.—If a tumor of the cord divides the spinal canal into two compartments, the lower of which is a cul-de-sac, the spinal fluid will usually show the very characteristic change known as the *Nonne-Froin syndrome.* In its fully-fledged form this consists of the following: (1) yellow coloration of the spinal fluid (xanthochromia), (2) a great increase in the protein without any corresponding increase in the cell count, and (3) spontaneous coagulation. Of these the second is much the most important, the third is seldom seen, and xanthochromia may occur in other conditions such as slight cerebral hemorrhage. The full syndrome, moreover, may be produced by any lesion, such as Pott's disease or a tumor of the spine, which will divide the canal into two segments. For a full discussion of the mechanism by which this peculiar condition is produced, reference must be made to monographs dealing with the cerebrospinal fluid.

When the spinal canal is blocked by a tumor there is naturally a marked fall in the pressure of the fluid in the cul-de-sac. This is shown by means of a double puncture, both cisternal and lumbar. The Queckenstedt reaction is no longer obtained; that is to say, there is no rise in the spinal fluid (lumbar) pressure when both jugular veins are compressed, although the cisternal puncture pressure rises normally.

HYDROCEPHALUS

Hydrocephalus was known to the ancients. But from the time when the father of medicine tapped the hydrocephalic ventricle down to the present

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day little has been added to our knowledge of the condition and practically nothing to its treatment, except that Magendie, Hilton, and others recognized the importance of obstruction to the exits of the cerebrospinal fluid in the roof of the fourth ventricle. Immense strides have been made, however, both in the diagnosis and the treatment of the disease, and these advances are largely due to the work of Dandy and his associates at Johns Hopkins Hospital.

The cerebrospinal fluid is produced in the ventricles and absorbed in the subarachnoid space covering the vertex of the brain. Anything which

Fig. 395.—Moderate degree of hydrocephalus due to obstruction in the aqueduct.

prevents the passage of the fluid from the place of production to the place of absorption will give rise to hydrocephalus.

The obstruction may occur at three points: (1) in the aqueduct of Sylvius, (2) at the foramina in the roof of the fourth ventricle, and (3) around the mesencephalon. The first two lead to *obstructive* hydrocephalus, the third to *communicating* hydrocephalus (Fig. 395), so called because free communication exists between the ventricles and part at least of the subarachnoid space. The anatomical changes depend entirely on the site of obstruction.

Fig. 396.—Ventriculogram of hydrocephalic ventricle, with separation of coronal suture.

Fig. 397.—Hydrocephalus. The ventricles are enormously dilated, and the substance of the cerebrum is reduced to a mere shell. The brain stem and cerebellum, however, were practically normal, so that the vital centers in the medulla were not interfered with.

In order to determine the type of hydrocephalus in any particular case Dandy introduced three tests. (1) Phenolsulphonephthalein when injected into the normal ventricle appears in the spinal fluid obtained by lumbar

puncture. This is also true for the communicating type of hydrocephalus, but not for the obstructive type. (2) When the spinal fluid is replaced at autopsy by India ink, the entire surface of the brain is stained with the pigment. In obstructive hydrocephalus the ink does not enter the ventricles, but reaches the surface of the cerebrum. In the communicating type the dye does not pass beyond the midbrain. (3) In the living patient air is used instead of India ink, being injected either into the spinal sac or into the ventricles. An X-ray picture will then show clearly the outline of the ventricles (Fig. 396) and whether the air has reached the sulci on the surface of the cerebrum. By this method the exact site of the obstruction can be determined with the greatest accuracy.

The cerebrospinal fluid after escaping through the foramina of Magendie and Luschka enters the basal cisterns, and passes forwards to the pontine and mesencephalic cisterns, whence it ascends through the narrow opening in the tentorium cerebelli to the upper surface of the brain, where practically all the absorption takes place. It therefore follows that any obstruction in the narrow waters around the midbrain will be followed by a damming up of fluid, and a distension not only of the basal cisterns but also of the entire series of ventricles (Fig. 397).

Fig. 398.—Hydrocephalus showing huge sac of fluid.

By plugging the aqueduct of Sylvius Dandy produced distension of the third and lateral ventricles. When the foramen of Monro on one side was blocked the corresponding lateral ventricle became dilated. If the choroid plexus was first removed before the foramen was plugged, the ventricle was found to be empty and collapsed, as the source of the fluid had been destroyed. Blocking of the foramina in the roof of the fourth ventricle by means of an artificially produced local inflammation resulted in dilatation of all the ventricles. Adhesions were produced around the midbrain by packing with gauze soaked in iodine, and the result was a typical communicating hydrocephalus with dilatation of basal cisterns, foramina of Magendie and Luschka, and the entire system of ventricles.

It is probable that meningitis is responsible for the adhesions which produce the vast majority of cases of hydrocephalus due to occlusion of the foramina of Magendie and Luschka. In some instances a definite history of meningitis can be obtained, in others it is indefinite or absolutely lacking. The adhesions are not necessarily in proportion to the

severity of the meningitis, and the occlusion depends rather upon the site than the number of the adhesions.

Stenosis of the aqueduct of Sylvius, although occasionally caused by the pressure of a tumor, is usually due to the formation of scar tissue. This is the principal cause of congenital hydrocephalus and a frequent cause of the cases occurring in infancy and early childhood. The stenosis may involve only a part or may occupy the whole of the canal. There may be only a thin veil of membrane across the lumen.

It is not possible to say with certainty what is the exact cause of this cicatricial tissue. Some cases are probably due to slight intrauterine inflammation destroying the epithelial lining of the canal. In others there may be a developmental origin, a *localized absence of ependyma allowing* adhesion of the walls by subependymal glial tissue.

Whatever be the type of the disease, and in whatever way it may be caused, the appearance of the patient is characteristic. The cranium is fearfully enlarged, dome-shaped, and surmounts the little wizened face like an enormous turban (Fig. 398). In the late stage the appearance is revolting, the head resembling a great quaking bag of jelly on which, here and there, can be felt the widely separated cranial bones. The cerebrum is thinned to a mere shell by the huge distension of the ventricles (Fig. 397), but the cerebellum and the vital centers at the base may be wonderfully intact. The intelligence is always affected, often to an extreme degree, but the condition, although usually progressive and ultimately fatal, may allow the patient to drag out a vegetative existence for a number of years. The end may come from rupture externally or from excoriation of the skin with a resulting meningitis.

Fig. 399.—Arnold-Chiari malformation.

An occasional cause of hydrocephalus is the *Arnold-Chiari malformation*. This is a congenital deformity of the hind-brain in which there is a displacement of parts of the cerebellum and brain stem through the foramen magnum into the upper part of the vertebral canal. It was first described by Arnold in 1894 and by Chiari in 1895, but the subject excited little interest until Russell and Donald in 1935 reported ten consecutive cases of spina bifida with myelomeningocele, all of which showed the

malformation and in eight of which hydrocephalus was present. The displaced structures form a tongue-like process and the fourth ventricle is greatly elongated (Fig. 399). Ogryzlo has reported seven cases from my department. The displaced tissue plugs the foramen magnum, and the hydrocephalus seems to be due to inability of the cerebrospinal fluid to pass around the brain stem and reach the cerebral subarachnoid space.

MENINGOCELE AND ENCEPHALOCELE

These conditions are much rarer than the corresponding condition in the spine. A meningocele is a protrusion of the meninges through a congenital defect in the skull. The dura and arachnoid mater are involved, so that the sac is an extension of the subarachnoid space, and is distended with cerebrospinal fluid. In an encephalocele the brain substance itself is extruded.

The two common sites are the occipital region and the frontal region close to the root of the nose; much rarer are the lower parietal region and the line of the sagittal suture; very rarely the protrusion is through the floor of the skull into the naso-pharynx where it may be mistaken for a polypus.

It is probable that there is a close causal connection between these conditions and hydrocephalus. The latter is often associated with cephaloceles, and the resulting pressure may well be responsible for a protrusion between the ununited bones of the infant skull.

Traumatic Cephalhydrocele.—In rare cases it happens that fracture of the skull in infancy is followed by the development of a cystic swelling at the seat of fracture. This is due not to a protrusion of the membranes, but to an actual escape of cerebrospinal fluid into the tissues, the result either of tearing of the arachnoid by the trauma, or laceration of the brain substance with opening up of the lateral ventricle. The swelling rapidly becomes larger, and the opening in the skull may increase in size to a remarkable degree owing to absorption of the bone.

HEAD INJURY

The frequency of automobile accidents has made injuries to the head a matter of great surgical importance. As a result of such injury there may be fracture of the skull, laceration of the brain, cerebral edema, intracranial hemorrhage, and the patient may present a clinical picture of concussion or compression.

Concussion.—Concussion is a condition of immediate and widespread loss of cerebral function following upon a blow to the head. The patient passes instantaneously into a state of profound shock in which both the higher faculties and the vital functions are so perilously suspended that he may appear to be on the very brink of death; yet recovery may be not only spontaneous but fairly speedy, although in many cases it is a much more long-drawn-out process. Consciousness is lost instantly, the patient falls like a log, is pale as death and covered with a cold clammy sweat. The temperature drops away below normal, the pulse is imperceptible, the respiration almost suspended. After a varying period a stage of reaction sets in, the temperature rises, the pulse becomes full and bounding. Recovery may be rapid, or the patient may manifest symptoms of profound irritability ("cerebral irritation") in which, as Erickson says, "it appears as if the temper, as much as or more than the intellect, were affected."

The lesions are variable and bear no direct relation to the clinical condition. There may be laceration of the brain, especially the under surface of the frontal and temporosphenoidal lobes. Instead of gross laceration

there may be widespread petechial hemorrhages, especially in those exposed to the explosion of a shell or bomb. In a smaller number of cases no lesion of any kind can be found in the brain.

The cause of concussion must be instantaneous and widespread. The only factor which appears to meet the demands of the situation is cerebral anemia. The skull is not the rigid incompressible structure which it is apt to appear. It may exhibit a remarkable degree of elasticity when subjected to pressure. The result of a blow is to produce a bending inward of the bone which in turn causes momentary but severe compression of the brain, so that the vessels in every part of the brain, medulla as well as cerebrum, are emptied, and a profound degree of cerebral anemia is produced. It may be, as Duret has suggested, that the cerebrospinal fluid is driven out of the lateral ventricles into the fourth ventricle with such force that it paralyses the cardiac and respiratory centers in the floor of that ventricle. This, however, is probably a factor of only secondary importance. The extensions of the subarachnoid space which, as will be shown presently, accompany the vessels into the depths of the brain and are filled with cerebrospinal fluid, feel the force of the fluid wave and, by giving way, may give rise to the minute petechial lesions already referred to.

The subsequent reaction is due to a refilling of the vessels, and the further clinical course will no doubt be largely influenced by the concomitant lesions present. The minute ecchymoses would not of themselves be sufficient to produce the train of symptoms such as headache, restlessness, and clouding of the mind which so frequently follow concussion, but they excite an inflammatory edema in their vicinity which is enough to give rise to a slight general cerebral edema and heightened intracranial pressure, with the series of disturbances which usually accompany that condition.

The multiple minute hemorrhages which are caused by injury to the vessel walls may be followed by gliosis not only in the superficial parts but also in the corpus striatum. Martland suggests that the dazed condition known as "punch-drunk" which sometimes afflicts pugilists in the course of a fight is due to injury caused by successive waves of cerebrospinal fluid. Old prize fighters often develop paralysis agitans (corpus striatum injury) or mental deterioration which may be attributed to post-traumatic gliosis.

Compression.—There is no organ in the body in which the effects of pressure are so serious as in the brain, owing to the fact that it is confined in a bony case incapable of expansion. It is true that a certain amount of elbow-room may be afforded by the flow of the cerebrospinal fluid from the cranial into the spinal cavity, but this is comparatively limited in amount.

Compression of the brain is produced by anything which will cause a rise of intracranial tension, such as hemorrhage, abscess, tumor, etc. The most important cause, however, is cerebral edema, which may complicate any of the above-mentioned lesions.

The effects are usually both local and general, although in such a condition as hydrocephalus (which may be taken for the moment as an edema of the ventricles), they are only general. At the seat of pressure the vessels are emptied of blood, whereas the vessels of the rest of the brain tend to

be dilated, all parts, however, suffering in their nutrition. The cerebro-
spinal fluid is driven as much as possible into the spinal canal. The pressure
then begins to affect the brain substance. The convolutions may be greatly
flattened, a condition seen in its most extreme form in internal hydro-
cephalus. The higher centers suffer first, so that consciousness is clouded
and finally lost. Pressure on the motor areas will first cause irritation with
convulsive movements, followed later by paralysis. The vagus and vaso-
motor centers in the medulla are stimulated; the pulse, therefore, is slow
and the blood pressure raised. Finally all the irritation phenomena are
replaced by those of paralysis.

Traumatic cerebral edema is a condition of the greatest importance. It
occurs as a more or less serious complication in 95 per cent of all severe
head injuries, whether or not there has been fracture of the skull. Fracture
of the base of the skull proves fatal because of the edema and hemorrhage
which accompany it; the mere fracture is of little importance.

The edema in the first instance is comparable with the edema which
follows trauma in any part of the body, and is of a true inflammatory
character. Soon, however, an edema of an entirely different nature devel-
ops; it is this which endangers the life of the patient, and it is due to
interference with the circulation of the cerebrospinal fluid.

The mode of production and absorption of the cerebrospinal fluid is
considered in detail in the previous section. Suffice it to say here that in
the main the fluid is produced within the ventricles by the choroid plexus,
escapes into the subarachnoid space through the roof of the fourth ven-
tricle, and passes up over the brain stem to be absorbed from the cerebral
subarachnoid space into the superior longitudinal sinus. Anything which
tends to obliterate that space and interfere with the absorption will
inevitably result in stasis of the cerebrospinal fluid and a general cerebral
edema.

The sequence of changes occurring in the circulation of the fluid as a
result of an acute cranial injury has been well described by Jackson, whose
account is summarized in the following paragraphs. As a result of some
form of trauma a local swelling of the brain soon appears at the site of
injury, and reaches its maximum in from 24 to 48 hours. If the local swell-
ing is only moderate in degree the interference with the absorption of the
cerebrospinal fluid will be correspondingly slight, and the parts will return
to normal in the course of a few days, although during that time the
intracranial pressure remains raised.

If, however, the local swelling is more marked, the general effects will
be the more serious. The brain is contained in a rigid, inexpansible box,
and the only compensatory mechanism to counteract the increased pres-
sure is the outflow of cerebrospinal fluid into the spinal canal. The cere-
bral hemispheres are pressed against the cranial vault, and the brain stem
is pushed downward into the incisura tentorii, as evidenced by downward
herniation of the hippocampal unci. Occasionally this downward herni-
ation from supratentorial edema may be sufficiently severe to compress
the posterior cerebral arteries and the oculomotor nerves. As the local
swelling increases, the cerebrospinal fluid is driven out of the cerebral
subarachnoid space into the corresponding space in the spinal canal, the
brain is pressed against the vault of the skull, the subarachnoid space is

compressed and obliterated, and the absorption of cerebrospinal fluid from that space stops completely. Circulation of the fluid ceases and stasis results. Meanwhile the choroid plexus continues to secrete cerebrospinal fluid, although perhaps more slowly, and the accumulating fluid in the basal cisterns pushes the brain still more forcibly against the cranial vault, still more effectually interfering with absorption. As the brain is pushed upward the brain stem tends to plug the narrow incisura tentorii, so that the fluid accumulates in the basal cisterns and distends the ventricles, producing a form of communicating hydrocephalus which is considered more fully in the section on hydrocephalus. The dilatation of the ventricles aggravates a situation which is already sufficiently hopeless, and pressure on the medulla develops, with death as the result.

At autopsy the dura is very tense, the convolutions are markedly flattened, and the sulci can be traced with difficulty. In the traumatic cases there is none of the great accumulation of fluid in the subarachnoid space over the cerebrum which is seen in the wet brain of alcoholism. The cut surface of the brain, however, is wet and pale, and a clear fluid exudes from it. The differentiation between grey and white matter is much less marked than usual. The brain, in short, is water-logged. The fluid in the perivascular spaces, which may be regarded as the lymph of the brain, is unable to escape into the subarachnoid space owing to the high cerebrospinal fluid pressure, and is therefore imprisoned within the brain. Microscopically the cortical cells show marked degeneration, and are widely separated by the edematous fluid, which also distends the perivascular lymph channels.

A subtemporal decompression merely allows any fluid already imprisoned in the subarachnoid space to gush out, and the brain then blocks the opening, thus effectually preventing any further escape of fluid. It is obvious that unless the vicious circle be broken by relieving the pressure below the tentorium by lumbar puncture there can only be one termination. The lumbar puncture should be done at the earliest possible moment and not delayed until symptoms of extreme pressure have developed, for the pressure on the brain speedily leads to anemia, which in turn is followed by destruction of tissue and gliosis. This is probably the chief cause of the late effects commonly known as traumatic neurosis. The danger of the medulla being forced into the foramen magnum, which is undoubtedly great in cases of brain tumor and which is frequently attended by fatal results, need not be feared in traumatic edema.

Laceration.—Varying degrees of laceration are common results of head injury. This may occur with or without fracture of the skull. Fracture, indeed, seems to act as a safety valve for the brain, as in a case which I observed of a child who fell on his head from a height of two stories and sustained a fracture of the skull which extended from the base over the vertex to the base on the other side, but suffered no permanent ill effects. Often the laceration is most marked on the side opposite to that on which the blow is struck, the condition known as *contrecoup*. Contrecoup injury, which is commonly seen on the under surface of the frontal lobes (Fig. 400A) and the temporal and occipital poles, may be more or less severe than the lesion at the site of the original injury. When the patient dies months or years later, cortical defects may be seen at the

summits of the convolutions with demyelinization and neuroglial scarring of the underlying white matter. These lesions, often small and easily over-looked, may be yellowish-brown in color due to the presence of old blood pigment. The acutely injured brain is swollen, a swelling usually attributed to edema, although some workers question this explanation. Petechial hemorrhages are common. Under the microscope they take the form of so-called ring hemorrhages, a ring of red blood cells around a central necrotic area. The lesions are really in the nature of hemorrhagic infarcts rather than true hemorrhages; blockage of a small vessel leads to necrosis, with diapedesis of red cells into the necrotic zone.

The neuro*glial reaction* to trauma has attracted much attention, both in the experimental animal and in man. All three glial elements, microglia, oligodendroglia and astrocytes, share in the changes. The *microglia* reacts to local destruction and disintegration of tissue. Transition forms of
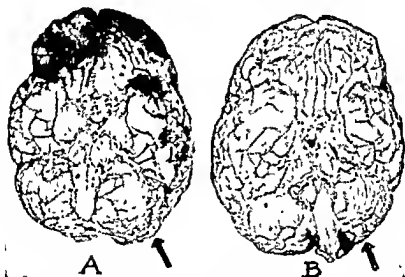
Fig 400.—Contrecoup injury: A, recent; B, old. Hemorrhagic laceration in A, post-traumatic atrophy in B. The site of the blow (arrow) was the same in both.

microglia are found within a few hours of laceration, but fully formed compound granular corpuscles, the scavenger cells of the central nervous system, only appear after three or four days; they remain as long as products of disintegration are present. The *oligodendroglia* reacts immediately after injury with enlargement and vacuolization of the cells; in a few hours there is acute swelling which persists for weeks, especially about the local injury. Acute swelling of the oligodendroglia is one of the commonest and least specific of glial reactions. It is found in every patient dying in coma. The *astrocytes* undergo regressive changes with the development of ameboid forms in the first few days after injury. In the zone nearest the injury there is complete destruction, but beyond this zone there is active proliferation, with cellular mitosis and the formation of a dense feltwork of fibrils. This gliosis persists indefinitely in the neighborhood of the lesion.

Partly as the result of tissue destruction, partly as the result of gliosis, a series of slow atrophic changes may follow the injury. The damaged part of the brain shrinks (Fig. 400B), and fluid collects in the subarachnoid space. This can be shown by the injection of air followed by roentgenography. The process may go on for a long time and be associated with great mental impairment. There may be epileptic seizures, due perhaps to interference with function caused by the extensive gliosis.

Hemorrhage.—Intracranial hemorrhage is one of the commonest results of head injuries. In some degree it is a more or less constant accompaniment of laceration of the brain. Although fracture of the base or vault of the skull is often present, it is important to realize that severe intracranial hemorrhage may occur *without* fracture. The types apt to occur without fracture are severe concussion hemorrhage (including "blast" injuries from bomb explosions), the chronic type of subdural hemorrhage
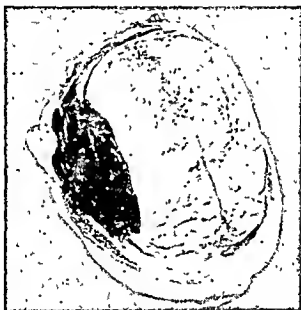
Fig. 401.—Extradural hemorrhage. A large blood clot lies outside the dura mater.

(chronic traumatic subdural hematoma), which is practically never associated with fracture, and contrecoup cortical laceration and hemorrhage. If the fracture of the base runs through the cribriform plate of the ethmoid, the accessory nasal sinuses, or the middle ear, meningitis may presently be added to hemorrhage.

Extradural Hemorrhage.—This is hemorrhage from one of the branches of the middle meningeal artery. There is usually fracture of the squamous portion of the temporal bone, but a fracture does not need to be present. The main division of the middle meningeal is the artery commonly involved either at the anterior inferior angle of the parietal bone or when traversing the squamous temporal, but the posterior branch is not immune. The elastic recoil of the skull under the blow produces an initial separation of the dura from the bone, a separation which gradually increases as blood is poured out. After a *lucid interval* of a few hours, symptoms of compression appear, and there may be evidence of pressure

on the motor area. Unfortunately the lucid interval may not be so lucid as to prevent the patient's arrest for drunkenness, and he may spend the night in a prison cell instead of on an operating table. A combination of drunkenness and middle meningeal hemorrhage is a possibility which must not be overlooked. After the lucid interval paralysis of the opposite side of the body develops. There is often dilatation of the pupil on the side of the hematoma due to stretching of the third nerve on that side as it runs forward below the hippocampal uncus, or to the nerve being pulled around the corner of the clivus of the sphenoid owing to the upper part of the brain stem being pushed to the opposite side by the hematoma so that a definite groove is left on the nerve. In rare cases the nerve may be pulled right out of the brain stem. The extradural blood is unable to reach the subarachnoid space, so that as a rule there is no blood in the spinal fluid. Blood, however, may be present from laceration of the cortex of the opposite cerebral hemisphere due to contrecoup. Unless treated promptly the condition usually proves rapidly fatal. At operation or autopsy a large clot is found between the dura and the bone (Fig. 401) and there may be great flattening or even indentation of the brain. The presence of blood in the spinal fluid makes the prognosis worse.

Subdural Hemorrhage.—Subdural hemorrhage differs from extra-dural hemorrhage in almost every respect. It is venous in origin, of slow development, the causal trauma is slight or trivial, and the late results may be extremely grave.

The injury is commonly in the frontal or occipital region, and is therefore applied in an antero-posterior direction. It may be so slight that the patient does not think of mentioning it. In one of my cases the patient bumped his head against a cupboard door. The long interval between receipt of the injury and the development of symptoms tends still further to hide the traumatic nature of the condition. In a series of cases examined in the division of neuropathology, University of Toronto, the average time between the injury and operative treatment was about four months. It is usually supposed that the cerebral veins passing to the sagittal sinus are ruptured owing to the brain suddenly being jolted backward or forward, but this explanation is open to question. Most cases occur in men over forty years of age. The neurological symptoms are varied, but the most important are severe headache, mental confusion, and somnolence increasing for weeks or months after a trivial trauma, symptoms which often give rise to a mistaken diagnosis of frontal lobe tumor. There is a striking absence of choked disc, and the spinal fluid pressure is normal, although the fluid may be slightly yellow. Tenderness in the temporal region may be an important sign. Linell, in an analysis of the late effects of chronic traumatic subdural hematoma in cases at the Toronto General Hospital, emphasizes the frequent development of serious mental deterioration either soon or long after the hemorrhage.

The hemorrhage may be *diffuse*, covering the greater part of one hemisphere, or, owing to rapid clotting of the blood, it may remain *localized* to one part of the subdural space, and may then give rise to definite localizing symptoms demanding operation. The localized form is referred to as *chronic traumatic subdural hematoma*. The blood seldom succeeds in spreading from one side of the brain to the other unless the injury

be at the base. Bilateral hemorrhage, however, is quite frequent owing to the injury produced on the other side at the point of contrecoup.

If the arachnoid is torn, as it is apt to be over the great cisterns at the base, the blood will escape into the subarachnoid space and will be found in the cerebrospinal fluid.

The *subsequent changes* which the clot may undergo are of importance. If death does not supervene, a limited amount of the blood may be absorbed, but the greater part becomes encysted. The clot becomes softened and liquefied so as to form a cyst, the walls of which consist at first of fibrin but later of a very tough fibrous membrane. The contents are brown or greenish, but in course of time the blood pigment is absorbed, and masses of cholesterin crystals take its place. The cyst can be stripped from the brain on the one side and from the dura on the other. As a result of the slow breaking down of the red blood cells with liberation of hemoglobin there is a gradual rise in the osmotic pressure in the liquefied clot, in consequence of which fluid is drawn into the cyst. The local pressure becomes ever greater, thus explaining the onset of symptoms suggestive of cerebral tumor weeks and sometimes months after the original injury.

In *intracranial hemorrhage in the newborn* the cerebral veins passing from the cerebral cortex across the subdural space into the superior longitudinal sinus are injured. There is no fracture of the skull, the trauma being due to the moulding of the head or the use of instruments, with as a subsidiary factor the strain thrown on the vessels by asphyxia or by efforts at artificial respiration. At autopsy in fatal cases tears are frequently found in the tentorium cerebelli or the falx cerebri. These lesions are easily overlooked unless special precautions are taken in the performance of the autopsy. The condition is most frequently met with in premature children and in breech presentations.

The blood is poured into the subdural space, but the arachnoid is frequently torn, so that blood is found in the cerebrospinal fluid. Lumbar puncture, therefore, is a valuable means of diagnosis. As the extravasation is most marked over the upper portion of the cerebral surface the leg centers are the ones to suffer most. A degree of hemorrhage which in an adult would certainly prove fatal can be compensated in the child by the elasticity of the skull and the safety valve action of the fontanelle.

Subarachnoid Hemorrhage.—There are two very different forms of hemorrhage into the subarachnoid spaces, spontaneous and traumatic: *Spontaneous* hemorrhage is due to rupture of a small (berry) aneurism on the circle of Willis or the middle cerebral artery, and does not concern the surgeon. Spontaneous subarachnoid hemorrhage may cause the patient to fall and hit his head; in such a case one must avoid the mistake of assuming that the hemorrhage is traumatic in origin. *Traumatic* hemorrhage is due to damage to the vessels in the subarachnoid space from fracture of the skull, or to laceration of the cerebral cortex as the result either of direct violence or of contrecoup injury. When the hemorrhage is into the large open cisterns at the base of the brain death soon results from pressure on the medulla. Over the cortex, on the other hand, the subarachnoid space is greatly subdivided by the numerous septa which traverse it, so that the blood infiltrates the network rather than forms a large and massive clot. In this variety blood is always present in the

cerebrospinal fluid. The characteristic yellow tinging of the fluid known as *xanthochromia* and due to hemolysis of the red blood cells appears within four hours and increases in intensity during the first week. It then gradually fades, and by the end of three weeks the fluid is colorless.

Intracerebral Hemorrhage.—This variety of hemorrhage may be due to spontaneous rupture of an artery in the interior of the brain, a condition of interest to the physician rather than to the surgeon. Or it may be traumatic in origin.

Traumatic hemorrhages, occurring as they frequently do as a complication or accompaniment of concussion, have already been alluded to. They are of two varieties.

1. Numerous small punctate hemorrhages scattered throughout the brain but most numerous in the basal ganglia. They are characteristically seen in cases where the skull is not fractured. They are apparently due to a sudden wave of cerebrospinal fluid which is driven by the blood from the subarachnoid space into the perivascular extensions of that space. The fibrillary extensions from the vessel wall to the perivascular sheath may be too forcibly stretched, thus injuring the vessel walls, but this may not be the correct explanation. A replacement gliosis follows the hemorrhages, and this may be the physical substratum of many of the postconcussion neuroses and psychoses. Martland has also suggested that the condition known to prize-fighters as "punch-drunk" is another example of the same condition. Many fighters who have been long in the ring develop corpus striatum symptoms which may suggest Parkinson's disease and may end in mental breakdown.

2. Larger hemorrhages the result of the laceration of the brain, and principally affecting the surface, although often extending for some distance into the interior. The laceration and hemorrhage are seldom below the area of skull which has received the blow; they are of the contrecoup type, usually at the tips of the frontal and temporal lobes as the result of a blow on the back of the head. Occasionally the only hemorrhage found is in the pons or midbrain due to impact of the pons against the basi-occiput. The brain stem must therefore be examined in every autopsy on a case of head injury. Such a hemorrhage consists of: (1) a central clot, (2) a zone of liquefying brain substance of a red color, and (3) an area dotted with minute hemorrhagic points. Ultimate cyst formation is very common, as in so many brain lesions.

A somewhat rare occurrence is the onset of symptoms of cerebral hemorrhage some days after the receipt of an injury to the head. This is supposed to be due to a focus of cerebral softening implicating a vessel and thus giving rise to a secondary hemorrhage.

It frequently happens that in a patient with a history of having fallen heavily on the head a large hemorrhage is found in the basal ganglia. This is a spontaneous hemorrhage from one of the branches of the middle cerebral artery, and the fall was the result and not the cause of the hemorrhage.

INTRACRANIAL SUPPURATION

Suppuration within the cranial cavity may take one of four chief forms: (1) extradural abscess, (2) meningitis, (3) cerebral abscess, and (4) sinus phlebitis.

Extradural Abscess.—Infection may spread inward from the skull and give rise to local suppuration between the bone and the dura mater. The primary seat of the infection is usually an osteomyelitis of the cranium, middle ear or frontal sinus disease, or a compound fracture of the skull. Reference has already been made to the important part played by thrombophlebitis of the diploic veins.

A localized collection of pus is formed external to the dura, and as the dura is remarkably impervious to infection it may be a considerable time before a general meningitis or a cerebral abscess complicates the picture. An interesting feature of the disease is the development of the condition described in so masterly a manner by Percival Pott in 1760 that it is still known as *Pott's puffy tumor* (Fig. 402). The scalp over the abscess becomes swollen, puffy and edematous in just the same way as does the skin overlying an osteomyelitis. If a wound of the scalp is present the inflammatory material is able to escape, and the puffy tumor as a rule does not form.

Infection of the subdural space (*subdural abscess and subdural empyema*) may complicate extradural infection. That this is not more common is due to the fact that a fibrinous exudate quickly seals the under-
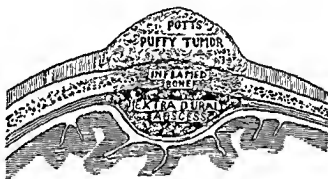
Fig. 402.—Pott's puffy tumor in extradural abscess.

lying subdural space by what MacEwen called a "soldering" process, which stitches together the intradural cleavage planes. The potential space between dura and arachnoid can be barricaded in a way not possible in the case of the subarachnoid space. Subdural abscess is usually the result of otitis media or sinusitis.

Acute Meningitis.—This is hardly the place in which to discuss the different varieties of meningitis, but it may be said that the organisms found in order of frequency are the meningococcus, the pneumococcus, and the streptococcus. Infection usually spreads from some neighboring focus such as the nasopharynx, the middle ear, the frontal sinus, a compound fracture of the skull, a patch of osteomyelitis, or a cerebral abscess. Meningitis may, in short, complicate any form of intracranial suppuration.

Meningitis may be a formidable complication of fracture of the base of the skull, particularly the anterior cranial fossa with involvement of the nasal fossae and ethmoidal sinuses. In such cases the fatal infection may come from infected sinuses through the fracture line years after the accident; in this interval the patient has been living, fortunately unwittingly, on the edge of a volcano. Linell and Robinson report a case in which a
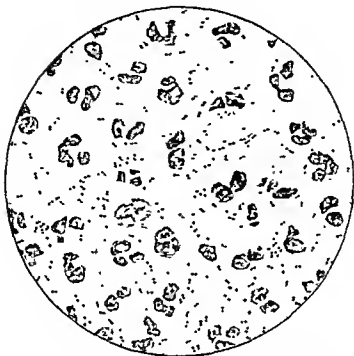
Fig. 403.—Cerebrospinal fluid in pneumococcal meningitis.
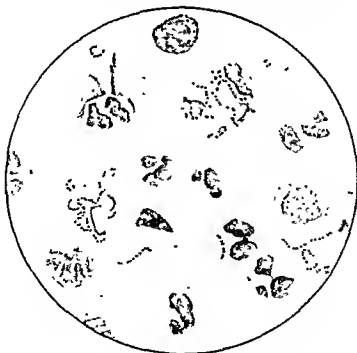
Fig. 404.—Cerebrospinal fluid in streptococcal meningitis.

pneumococcal infection spread from acutely infected ethmoidal and sphenoidal sinuses through the site of a fourteen-year-old fracture in the cribriform plate of the ethmoid, and caused a fatal meningitis. There are pension possibilities in such an occurrence.

The final diagnosis is made by means of lumbar puncture. The cerebrospinal fluid under pressure, and of varying degrees of turbidity, shows a great increase of protein, and is crowded with pus cells. In the pneumococcal and streptococcal forms the organisms can usually be found in large numbers in the direct smears (Figs. 403 and 404). In the acute cerebrospinal meningitis due to the meningococcus it is sometimes impossible to find any diplococci in the smears, and culture must be resorted to.

Abscess of the Brain.—A cerebral abscess is never primary, but always secondary to some other focus of infection. These abscesses can be divided into two groups: (1) Those which arise from a local focus such as the

Fig. 405.—Abscess of temporal lobe.

middle ear, frontal and ethmoid sinuses, depressed fracture of the skull, etc.; these are single, there is no smell, and the odds are even on recovery. (2) Those in which the infective material comes from a lung abscess; these are often multiple, very foul smelling due to a mixture of organisms including anaerobes, and are practically always fatal. In any general pyemia there may be numerous small pyemic abscesses in the brain. The staphylococcus produces multiple small yellow "boils" in the superficial cortex with a hyperemic zone around them.

The relation of lung abscess and bronchiectasis to brain abscess is difficult to explain, for the abscesses are confined to the brain and not infrequently they are single, thus differing sharply from ordinary pyemic abscesses. A possible explanation in some cases is that the lung abscess and the brain abscess may have a common origin in an infected nasal accessory sinus. This idea is supported by the fact that the abscess is often in the frontal lobe.

The most important cause of brain abscess is middle ear disease. The infection does not pass in through the internal auditory meatus, but either upward through the tegmen tympani, or along the veins into the substance of the brain. In the former case the path of infection can be readily traced, for the bone is eroded and there is a mass of granulation tissue between the dura and the bone. It is remarkable how often there is no general meningitis; although the infection must traverse the subarachnoid space, the adhesions which form are sufficient to prevent a general spread.

When the infection spreads by the veins, or it may be by the lymphatics, the surface both of the bone and of the brain may appear perfectly healthy.

Fig. 406.—Chronic abscess of brain due to shrapnel wound. Perforation into lateral ventricle can be seen.

The lower part of the temporo-sphenoidal lobe is the seat of election in the middle ear cases (Fig. 405), although the cerebellum is affected in a certain number of cases. An abscess in the former situation may remain "silent" as regards localizing signs, or it may give rise to paralysis. If the abscess extends upwards first the face, then the arm, and finally the leg may be affected, owing to the gradual involvement of the cortical centers which are arranged in that order. If it extends inwards first the leg, then the arm, and finally the face are involved, since the fibers in the internal capsule are arranged in that order from behind forward.

A cerebral abscess is usually single, but may be multiple, especially when due to pyemia. In the acute stage the surrounding brain tissue is inflamed, soft, and infiltrated with pus. Later, if the patient does not die,

a well-marked capsule of fibrous tissue may form around it which effectually prevents either spread or absorption of the toxic products. It is usually six weeks before such a capsule is produced. Cerebellar abscess secondary to otitis media is one of the most serious forms, because of the frequency of meningitis, a complication probably due to the depth of the cerebellar folia. The mortality, even with operative treatment, is about 80 per cent compared with a 40 or 50 per cent mortality from temporal lobe abscess.

The contents of the abscess are greenish in color, perhaps tinged brown with blood, and often of an offensive odor. Staphylococci, streptococci, and pneumococci are perhaps the organisms most frequently found, but many other varieties may be present, amongst which may be mentioned B. pyocyaneus.

The cerebrospinal fluid is unaltered, apart from increased pressure and a trace of globulin, a point of great value in differentiating abscess from meningitis. In abscess, moreover, there are not the same signs of septic absorption as are found in meningitis, the temperature may be normal or subnormal, the pulse is abnormally slow, and the leucocytosis in the blood is moderate compared with the hyperleucocytosis of meningitis.

The chronicity of some brain abscesses is remarkable. A localized collection may remain in the brain for many months producing wonderfully little disturbance. Eventually, however, it will almost always rupture into the ventricles or on to the surface, where it produces an acute and fatal meningitis. In war wounds the presence of a foreign body in the brain not infrequently gave rise to a cerebral abscess quite a long time after the initial injury. In the University of Manitoba Pathological Museum there is a brain showing a tiny abscess of the frontal lobe which had ruptured into the lateral ventricle (Fig. 406). Leading from the abscess to the surface a long scar marking the track of the original missile stands out prominently. Two years elapsed between the time the man was wounded and the date of his death due to the abscess bursting into the ventricle, and during that period he only suffered from frontal headaches, dizziness on stooping, and a rare convulsive seizure, so that the presence of an abscess was entirely unsuspected.

Sinus Phlebitis.—The dura mater lining the skull consists of two layers which separate in places to enclose the cranial venous sinuses. These may become inflamed and thrombosed owing to the spread of infection from some neighboring focus. It is the same story that has already been repeated several times, and which need not be recapitulated in detail once more.

In brief, by far the commonest cause is inflammation of the middle ear, which spreads to the *lateral sinus*. The *superior longitudinal sinus* is infected from erysipelas and other septic conditions of the scalp, or from a compound fracture of the skull. Infection may reach the *cavernous sinus* from suppurative conditions in the face, nose, orbit, and sphenoidal air cells. Carbuncle of the face is regarded as a special black sheep in this respect. The routes of infection are the facial vein to pterygoid venous plexus to cavernous sinus, or angular vein to ophthalmic veins to cavernous sinus. Cavernous sinus thrombosis is often bilateral, the infection passing to the other side by way of the circular sinus.

When infection reaches such a vessel as the lateral sinus, the endothelial

lining becomes inflamed and roughened, and thrombosis occurs so that the vessel feels solid. The thrombus being a septic one, softening and liquefaction soon occur, and there is thus a tendency for septic particles to be carried off in the blood stream first to the lungs, where they set up numerous septic infarcts, characterized by sudden attacks of pleuritic pain and perhaps coughing of blood, and later throughout the body.

The thrombosis tends to spread down the internal jugular vein as well as to the other sinuses, and the vein may be felt as a hard and tender cord in the neck. This tendency for the thrombosis to spread, although disastrous in some ways is yet beneficial in others, for the thrombotic process which occludes the vessel usually succeeds in keeping ahead of the liquefaction process which renders the clot so dangerous, so that there may be a considerable area of liquefied clot in the vessel, a veritable abscess, which is nevertheless securely shut off from the general circulation. The sword of Damocles, however, is suspended by a very thin thread, and disaster may overtake the patient at any moment.

The infection may spread outward, if it has not already come from that direction, and give rise to a fatal general meningitis, or in some cases a cerebral abscess. Or, as already mentioned, it may spread downward into the jugular vein or forward into the other sinuses. In a recent autopsy the lateral, petrosal, and cavernous sinuses on both sides were filled with a septic semi-liquid clot, the infection having crossed to the other side via the circular sinus. The jugular vein had been ligatured, so that no downward spread was possible.

The *clinical picture* of sinus thrombosis is very different from that of cerebral abscess. The course of the former is stormy and tempestuous compared with the comparative calm and peace of the latter. The relation to the blood stream is, of course, amply sufficient to explain the difference in the two cases.

INTRACRANIAL TUMORS

Tumors within the cranial cavity may be divided into two great groups: intracerebral and extracerebral. The intracerebral group comprises the gliomas, metastatic carcinomas, and a few miscellaneous tumors such as hemangiomas. The extracerebral group, far more favorable from the surgical standpoint, comprises the meningiomas, acoustic neuromas, and tumors of the pituitary region. An analysis of 100 consecutive cases examined by Linell at the Banting Institute gives the following figures: (A) extracerebral, 23: meningioma, 9; acoustic neuroma, 8; pituitary region tumors, 6; and (B) intracerebral, 77: glioma, 54 (glioblastoma, 29; astrocytoma, 15; medulloblastoma, 7; oligodendroglioma, 3); metastatic carcinoma, 8; miscellaneous group (ependymoma, hemangioma, etc.), 15.

Secondary Effects.—Any intracranial tumor is liable to produce secondary effects on the brain tissue, on the circulation of blood and cerebrospinal fluid, and on the skull. These are best seen in cases of intracerebral tumor.

The **brain tissue** in the neighborhood of the tumor shows atrophy from pressure. The irritation of the tumor may lead to a condition of edema not only in the immediate neighborhood but sometimes involving an entire cerebral hemisphere, thus accounting for the general enlarge-

ment of a hemisphere which is frequently observed even when the tumor is comparatively small. The most important complication of cerebral tumor is the increased intracranial pressure, and much of this increase may be due to edema. In fracture of the skull cerebral edema occupies a similar position of commanding importance; it is the edema rather than the fracture which eventually proves fatal. Secondary hemorrhage into a soft glioma is of frequent occurrence, and may be precipitated by the rash withdrawal of too large an amount of cerebrospinal fluid by lumbar puncture. The symptoms produced are those of apoplexy.

Stopford has suggested that the increased intracranial pressure is due to pressure on the great vein of Galen as it curves around the splenium of the corpus callosum. Tumors of the midbrain and pineal, situated so as to cause compression of this vein, are often associated with high intra-

Fig. 407.—Effect on the brain of a decompression operation.

cranial pressure, but a more probable explanation is that they act by exerting downward pressure on the aqueduct of Sylvius, and this is also true of other brain tumors.

Supratentorial tumors tend to force the brain stem down into the incisura of the tentorium, and the peduncle of the midbrain on the side opposite the tumor may be pressed against the free edge of the tentorium so as to become notched (Kernohan's notch). The result of this contralateral pressure may be pyramidal tract paralysis on the same side as the tumor and this is apt to cause wrong localization.

The operation of decompression has as its object the relief of intracranial pressure by the production of cerebral hernia (Fig. 407). The brain is allowed to protrude under the temporal muscle or the occipital muscles. But this protrusion does not necessarily mean a relief of intracranial pres-

sure. If the pressure is due, as is so often the case, to an obstructive hydrocephalus, a decompression is worse than useless. As Dandy remarks, if surgeons would picture at operation the brain under a decompression several months after the operation, they would hesitate about performing the operation so casually. The temporal and occipital muscles must by their contractions continually irritate the protruding portion of the brain, so that adhesions form between the brain and the overlying muscles, fluid collects between the adhesions, the vessels are injured, and the brain undergoes softening.

The *circulation* of the brain must inevitably be interfered with. When examined at operation the convolutions are flattened (Fig. 408), and none of the normal pulsation can be seen. The possibility of hydrocephalus must always be considered. If a symmetrical hydrocephalus can be demonstrated by means of cerebral pneumography, the tumor must obstruct a channel between the aqueduct of Sylvius and the foramen of Magendie. In such a case, of course, there would be no object in performing an explor-

Fig. 408.—Flattening of the convolutions in a case of cerebral tumor.

atory craniotomy. The subarachnoid space communicates normally with the lymph spaces in the sheath of the optic nerve, and the effect of fluid being forced into these spaces under high pressure is to obstruct the venous return along the nerve although still leaving the artery open, with the resulting edema and hemorrhage characteristic of choked disc.

The *skull* may be thinned in places from pressure, although as a rule this is seen in children rather than in adults. In the roentgenogram there may be a mottled ("beaten silver") appearance corresponding to the cerebral convolutions. Or there may be a localized thinning, due to direct pressure of the tumor. In meningiomas the local hyperostosis which often occurs over the tumor is practically pathognomonic. Tumors of the base may produce marked destruction. I have studied a case of pituitary tumor in which the floor of the sella turcica was occupied by a yawning cavity communicating with the nose. When the patient sat up in bed a clear watery fluid used to drop from his left nostril, an example of cerebrospinal rhinorrhea.

The Cerebrospinal Fluid in Brain Tumor.—There are no constant findings of real diagnostic value in the cerebrospinal fluid in brain tumor. It is true that the pressure is usually raised, but it must be remembered that a high cerebrospinal pressure is encountered in other conditions such as uremia, and that the state of the discs is quite as sensitive and reliable an indication of high pressure *as* is the manometer. The protein content is usually increased, sometimes to more than twice the normal amount. Ayer has pointed out that this increase is particularly constant and marked in tumors of the nervus acusticus. When everything is taken into consideration it appears to the writer that the information provided by an examination of the cerebrospinal fluid in cases of suspected brain tumor does not justify the quite considerable risk of fatal medullary compression which may follow lumbar puncture.

Brain Tumor and Trauma.—The question of the relation of trauma to brain tumor (particularly glioma) is of importance in pension and compensation cases. It is not possible to deny that in some isolated case there *might* be some causal connection between head injury and brain tumor, but probability must be based on the analysis of a large series of cases either of head injury or of brain tumor. In such a series no convincing evidence will be found of any relationship between head injury and glioma. The enormous amount of trauma to the head during the last war was not followed by any increase in the incidence of gliomas. This in itself would appear to be a crucial test. Parker and Kernohan, indeed, came to the anomalous conclusion that, statistically speaking, trauma seems to prevent rather than cause glioma. There does, however, appear to be a relationship between injury to the head and meningioma, for such a tumor not infrequently develops at the exact site of a previous injury.

GLIOMA

The group of the gliomata is the largest and the most important group of cerebral tumors. We use the word group advisedly. Malignant tumors of the brain used to be divided into sarcomas and gliomas. The sarcomas have now practically disappeared, but the gliomas have become subdivided into a bewildering number of classes, largely owing to the work of Bailey and Cushing. These authors recognize fourteen subgroups of the gliomata, the differentiation being achieved largely by the use of the newer histological methods of staining the neuroglial elements introduced by Ramón y Cajal, del Rió Hortega, and other members of the brilliant Spanish school of neurohistologists. It remains to be seen if this minute subdivision is desirable or will stand the test of time. Changes in the nomenclature are sure to occur. Meanwhile, as Ewing remarks, it appears premature to urge the full adoption of this very complex classification; better rather "to wait the time when general usage has made its selection of terms and classes."

At the same time it must be understood that the contribution of Bailey and Cushing is of fundamental importance. Not only have they demonstrated that the subgroups of the gliomata differ from one another in their histological structure; they have also shown that these differences correspond to great variations in the malignancy of the tumors. At one end of their list of 492 gliomata they have a group (medullo-epithelioma) in

which the average survival period was 8 months, whilst at the other end there is a group (astrocytoma fibrillare) in which the average survival period was 86 months.

In studying any large group of cases it will be found that they fall into three great classes: (1) globalstomas, (2) astrocytomas and (3) medulloblastomas. These will form the basis of the present discussion. Reference will be made to other rarer forms and subdivisions. Perhaps the chief
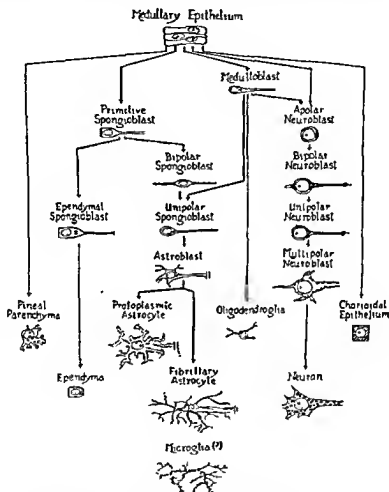
Fig. 409.—Schematic representation of development of the cells of the central nervous system. (Percival Bailey.)

stumbling block to an understanding of the new classification is the question of nomenclature. This is based upon the earlier forms of cells which appear in the development of the central nervous system, so that a brief account of these forms becomes necessary.

The medullary epithelium gives rise to two main types of cells, the spongioblast and the germ cell (Fig. 409). Some of the spongioblasts collect around the lumen of the neural tube, and become the ependymal cells lining the ventricles. Others migrate outwards and pass through a

series of stages of development into astroblasts and later into astrocytes, the classical neuroglial cells. Two types of astrocytes are recognized, the protoplasmic astrocytes with cytoplasmic processes and the fibrillary astrocytes with an abundance of fine fibrils. The astrocytes and the astroblasts are characterized by their affinity for gold (as may be shown by the Cajal gold sublimate method) and the possession of a process known as a "sucker foot," which is apparently attached to the wall of a capillary vessel.

The germ cell gives rise to two types of cell, the neuroblast and the medulloblast. The neuroblast develops into the neurone or adult nerve
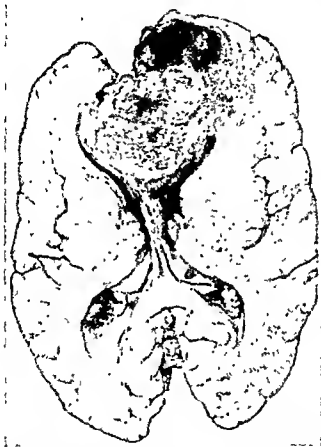
Fig. 410.—Glioblastoma multiforme of frontal lobe extending into corpus callosum.

cell; both have an affinity for silver. The medulloblast has no affinity for either silver or gold; it gives rise to an adult type of neuroglial cell known as oligodendroglia, so called because it possesses few dendritic processes and these few are extremely difficult to stain; there are no sucker feet.

By the use of suitable histological methods it is possible to identify all of these cells and many others in members of the glioma group of tumors, and these have been used by Bailey and Cushing as the basis of classification. We shall content ourselves with the three main groups above mentioned. Into one of these three a surgeon or a pathologist will be able to put the great bulk of his material.

Glioblastoma.—This tumor, which used to be called spongioblastoma, is the commonest and the most malignant of the gliomata. It corresponds to the gliosarcoma of the older literature. It constitutes about one third of Cushing's cases. Two varieties are recognized, glioblastoma multiforme, so called because of the variety in the shape and size of the cells and their nuclei, and glioblastoma bipolare, the cells of which when stained by gold sublimate are seen to possess one process, giving them a pear-shaped appearance. The glioblastoma is a tumor of middle life. It almost invariably occurs in the cerebral hemispheres. It does not metastasize to distant parts nor does it invade the meninges, but it spreads widely from its point of origin. In Cushing's five unoperated cases the average duration of life
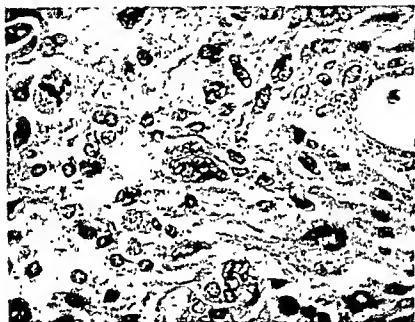
Fig. 411.—Glioblastoma multiforme showing great variation in cell type, tumor giant cells, a mitotic figure, and hyperplasia of vascular endothelium. × 500.

was only three months. Neither wide operative removal nor saturation with X-rays prevents recurrence of the growth.

The *gross appearance*, as Carmichael points out, is apt to be deceptive for it often gives the impression of being easily enucleated. This apparent encapsulation is due to degeneration of the central portion, leaving a peripheral zone of condensed tumor tissue. The tumor is soft, very vascular, as a rule fleshy in color, and often shows evidence of degeneration, gross hemorrhage, and cyst formation (Fig. 410). These tumors are not infrequently multiple.

The *microscopic appearance*, although varied, is distinctive. The tumor is highly cellular, and the cells are characteristically pleomorphic, varying greatly in shape and size, thus justifying the name "multiforme" which is applied to the common form of glioblastoma (Fig. 411). This pleomorphism is reminiscent of the varied cytological picture in an osteo-

genic sarcoma of bone. The cells are spongioblasts, that is to say incompletely differentiated glial cells, some of which are round or oval, others pyriform, and still others so large as to constitute true giant cells. The absence of glia fibrils is one of the characteristic features which distinguish it from the astrocytoma, the other great group with which it is liable to be confused. The tumor is often extraordinarily vascular, so that the frequent hemorrhages are easily understood, as are the troubles of the surgeon who tries to remove one of these tumors. Sometimes the vessels show marked proliferation of the endothelium with narrowing of the lumen; sometimes the adventitia is thickened. The surrounding brain tissue is often markedly edematous, and immediately around the tumor there is usually a well marked gliosis.
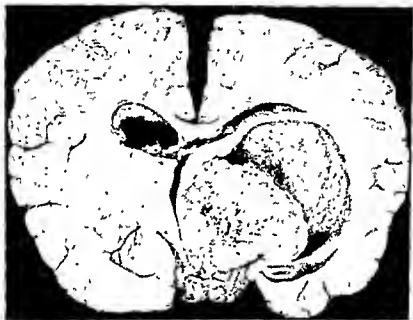
Fig. 412.—Astrocytoma with cyst formation.

Astrocytoma.—In this group we shall consider three tumors which are put into separate classes by Bailey and Cushing, namely the astroblastoma, the astrocytoma protoplasmaticum, and the astrocytoma fibrillare. These together formed 125 of Bailey and Cushing's cases as compared with 109 glioblastomas. Now the average survival period of theses cases after operation is over 70 months, that is to say 6 years. Many of the patients have lived very much longer and appear to be completely cured. From these figures it becomes evident how important is the determination of the general tumor type from the point of view of prognosis. A distinction must be drawn between the astrocytoma of the cerebrum in adults and the astrocytoma of the cerebellum in children. The latter is a pure astrocytoma, often undergoes cystic degeneration, and is the most satisfactory glioma known to the surgeon. The astrocytoma of the cerebrum in adults, on the other hand, is often highly cellular and shows mitotic figures. Scherer has pointed out that these tumors are often not pure

astrocytomas, but on thorough examination at autopsy show areas identical in form with glioblastoma multiforme, although these are seldom seen in surgical biopsies. These tumors must therefore be regarded with some degree of suspicion.

The tumor is seldom so well demarcated from the surrounding brain tissue as is the glioblastoma; indeed it may be difficult to be certain that a tumor is present except for the general increase of the white matter on one side. The tumors appear to be about equally frequent in the cerebrum and cerebellum, but the cerebellar cases mostly occur in children. Cyst formation is of common occurrence (Fig. 412), although Carmichael found no example of it in his six cases. Many cerebellar cysts are of this nature. Only a small nubbin of tumor tissue may be left projecting from the bottom of the cavity.
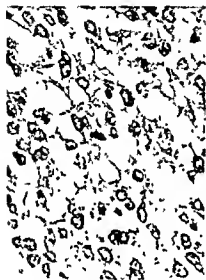
Fig. 413.—Astrocytoma, uniform cell type. × 630.

The *microscopic picture* is much less cellular than that of the glioblastoma. At first glance there may appear to be little difference from normal white matter. The cells which in hematoxylin and eosin preparations are small and round, are remarkably uniform in size, very different from the pleomorphism of the glioblastoma multiforme (Fig. 413). They are separated by a dense network of firm glia fibrils which are well shown by phosphotungstic acid hematoxylin, but are best demonstrated in gold sublimate preparations. There is none of the great vascularity so characteristic of the glioblastoma, nor do the vessels show any endothelial proliferation. In the surrounding brain tissue there is a complete absence of gliosis, and it is often impossible to tell where this tumor ends and the normal tissue begins.

Medulloblastoma.—This is the third of the great groups. The tumor nearly always occurs in children, and usually in the midline of the cerebellum, that is to say in the roof of the fourth ventricle (Fig. 414). It is quite as malignant as the glioblastoma, often invading the subarachnoid space in a diffuse manner, giving rise to the condition known in the literature as sarcomatosis of the meninges. Its high grade of malignancy is understood when we recall that the medulloblast is one of the primitive cells to which the germ cell gives rise, eventually developing into oligodendroglia. The embryonic nature of the growth explains another feature, the manner in which it responds for a time to radiation. As these children frequently suffer from a terminal paralysis due to metastasis in the spinal subarachnoid space, it is important that radiation treatment should include the spine.

The *gross appearance* is that of a soft reddish-grey mass growing in the midline of the cerebellum, and often filling the cavity of the fourth

ventricle. Hydrocephalus is naturally a frequent occurrence owing to the position of the tumor.

Microscopically the tumor is highly cellular, resembling a round cell sarcoma. All the cells are uniform in appearance, in contrast to those of the glioblastoma (Fig. 415). Although most of the cells are round, some are elongated or carrot shaped. These may be grouped in circular fashion, so as to give an appearance of pseudo-rosettes. These differ from the rosettes of the ependymomas in that there is no lumen in the center. There are no intercellular fibrils, thus differing from the astrocytoma. The medulloblast has no affinity for gold, again contrasting with the spongioblast and the astrocyte.

Fig. 414.—Medulloblastoma. The tumor is growing from the midline of the cerebellum and has invaded the fourth ventricle.

In view of the fact that a tumor in the roof of the fourth ventricle of a child may be the extremely malignant medulloblastoma or the extremely innocent astrocytoma, biopsy confirmation of the tumor type is of great importance in every case. In the former, attempt at operative removal is probably unwise because of the danger of spreading tumor cells into the subarachnoid space; in the latter the prospect of successful removal is excellent.

Metastatic Tumors.—When a diagnosis is made of tumor of the brain it must not be forgotten that the tumor may be secondary. The common primary sites are breast and lung, followed by hypernephroma, malignant melanoma of the skin, and less frequently cancer of the colon and the generative organs. The secondary tumors are often multiple. They are

more sharply circumscribed than the gliomas, and can usually be recognized from the gross appearance. The course of the disease is apt to be more acute than is the case with glioma. *Diffuse involvement of the meninges* may be the result of invasion of the subarachnoid space by a medulloblastoma or a metastatic tumor (often a glioma); sometimes the melanoma seems to originate in the meninges. A mantle of tumor cells may cover the brain and even the cord so that to the naked eye the appearance is that of meningitis rather than neoplasm. Tumor cells may be found in the spinal fluid during life.

Pinealoma.—This rare tumor arises from the pineal body. The microscopic picture is characteristic, consisting of groups of large cells with extremely large vesicular nuclei and also numerous small cells like lymphocytes (Fig. 416). The tumor usually occurs in the second decade. Owing to its anatomical position it compresses the aqueduct, causing dilatation of the ventricles and early headache. Other local symptoms are oculomotor

Fig. 415.—Medulloblastoma. × 240.

palsies and deafness. These tumors are the most inaccessible of all cerebral neoplasms.
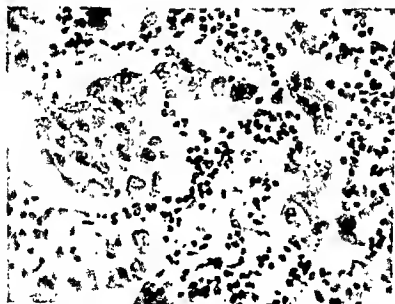
Fig. 416.—Pinealoma, showing the characteristic mingling of two types of cells. × 400

Ependymoma.—This uncommon tumor may be mentioned here, because it has a number of features in common with the medulloblastoma. It also is a tumor which occupies the fourth ventricle, arising either from the floor or the roof (Fig. 417). It is pale

Fig. 417.—Ependymoma. The tumor arises from the pons and occupies the entire fourth ventricle.
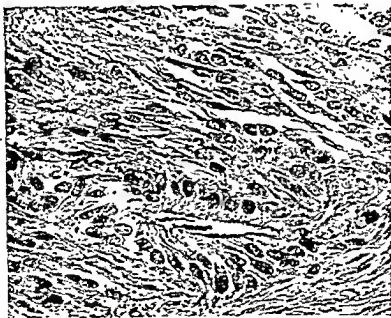
Fig. 418.—Ependymoma. The tumor cells are grouped around a definite lumen. × 500.

and firm compared with the soft rapidly growing medulloblastoma. It may occasionally occur elsewhere as in the septum lucidum. The more primitive types (ependymoblas-

toma) occur in the first decade, the more adult types (ependymoma) in the second and third decades. The tumors are of slow growth, and, apart from their position, of low malignancy.

Microscopically the tumor is composed of cells with the characteristics of ependymal cells. These cells, it will be remembered, are formed by the inward movement of spongioblasts. Many of them are grouped around small canals, giving an appearance of true rosettes (Fig. 418). Between the nucleus and the lumen the cytoplasm may contain tiny rods known as blepharoplasts, which are characteristic of ependymal cells. Many of these cells are ciliated.

Retinoblastoma.—Reference may here be made to the interesting tumor commonly known as glioma of the retina (Figs. 419 and 420). It presents three striking clinical characteristics: (1) it is bilateral in over 20 per cent of the cases; (2) over 90 per cent of the cases occur before the fourth year, so that the disease may be regarded as a congenital; (3) it displays a most remarkable familial tendency. Newton reports a family of 16 children of whom 10 died of this tumor, 7 of the cases being bilateral.

The exact nature of the tumor is still in doubt. It was Virchow in 1864 who gave it the name of glioma, by which it is still commonly known. It is not possible to demon-

Fig. 419.—Retinoblastoma.

strate glia fibrils by any of the ordinary methods, and there seems to be no good reason for preserving the name glioma. Flexner, who studied the condition in 1891, gave it the name of neuroepithelioma, and described circles or "rosettes" of columnar cells. By Mallory and others it is regarded as a neuroblastoma of the same nature as the tumors of nervous origin which arise in the anlage of the sympothetic system, more particularly in the adrenal medulla.

As the tumor is not composed of retinal cells, either glial or nerve cells, but of cells that started from the retinal anlage of the embryo and never developed into functioning cells, it appears best to use the term retinoblastoma. The tumor is composed of small round cells, which consist almost entirely of naked nucleus, with practically no cytoplasm and no fibrils. The rosettes are often absent; when present it appears probable that they are merely inclusions of cells having a tendency to develop into normal rods and cones. In some cases there is a perivascular mantling of living cells, those farther away from the vessels dying and failing to take up the nuclear stain.

The tumor is locally destructive and invasive, but in the later stages it may set up secondary growths in lymph nodes and internal organs. In one of my cases the liver was greatly enlarged, and was simply riddled with metastatic nodules.

Meningioma.

Meningioma.—This is the commonest of the extracerebral intracranial tumors. In Cushing's series there was one meningioma to every four gliomas. The name is a conveniently noncommital one. It used to be called dural endothelioma, but it does not arise from the dura nor is it an endothelioma. Its site of origin is the arachnoid mater, in those groups of mesothelial cells which are found in connection with or close to the arachnoid villi. Different views are held as to its exact nature. Penfield adopts Mallory's term, arachnoid fibroblastoma. The favorite anatomical sites are parasagittal (usually near the superior longitudinal sinus in the frontoparietal region), the olfactory groove, and the sphenoidal ridge. Occasionally it may arise from the arachnoid at the point of emergence of one

of the spinal nerve roots. Cushing lays stress on the part which trauma to the head plays in the production of many of these tumors. In one of our cases the tumor developed in the line of a fracture of the skull. But one swallow does not make a summer, and any claims as to a causal relation between trauma and tumor must be accepted with great reserve.

The tumor is firm in consistence in comparison with the gliomas. It may grow into the brain to such an extent that it may appear to be completely surrounded by cerebral substance and show no obvious connection with the arachnoid, but it never really perforates the pia. Usually it is well encapsulated, so that it can be readily shelled out in the postmortem room (Figs. 421 and 422). The overlying bone is usually vascular and may contain large blood sinuses. Vessels pass from the bone into the tumor. The dura is very vascular and bleeds readily. These features make the removal of a meningioma a more serious undertaking than the surgeon would guess from an inspection of a specimen in a museum jar.

Fig. 420.—Glioma of retina. (Ewing.)

Microscopically it consists of elongated cells which often show a very characteristic whorled arrangement (Fig. 423). Mallory considers these cells to be fibroblasts. The cells may undergo hyaline degeneration and form spherical masses like cell nests. Lime salts may be deposited in these masses, a condition to which the name psammoma has been applied. Bailey and Bucy have described a number of types of meningioma, such as the fibromatous (the common one), angioblastic, osteoblastic, sarcomatous and lipomatous. The last named presents a remarkable picture of fat-filled cells.

One of the most interesting features of the meningeal endotheliomas is the occurrence of *local changes in the skull* overlying the tumor. These changes may be of two types—local erosion or local bony thickening. Erosion, with, it may be, perforation of the skull, is of rare occurrence. Local bony thickening is much more common (Fig. 424). Cushing found cranial hyperostosis in 25 per cent of 80 cases of meningeal endothelioma. The

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hyperostosis is due to penetration of the dura and direct invasion of the skull by the tumor. Phemister has shown that the new bone is not tum-
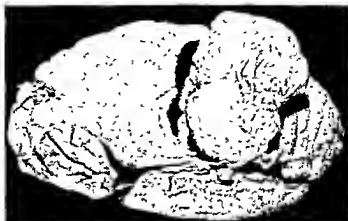
Fig. 421.—Meningioma. The encapsulated nature of the tumor and the depression in the brain are well shown.

Fig. 422.—Meningioma showing effects of pressure on the brain.

orous in nature, but merely the ossified stroma of the invading endothelioma which permeates both the inner and the outer tables of the skull.

The tumor is an innocent one, in a superficial location, and often characterized by the peculiar bony changes just described. The brain surgeon therefore prays for such a chance. As Cushing remarks: "There is today
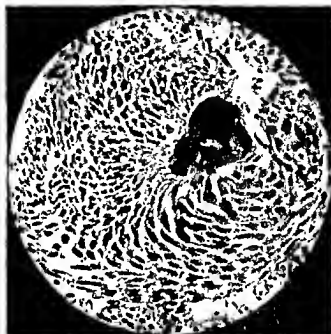
Fig. 423.—Meningioma. The elongated cells show a whorled arrangement around a central blood vessel. × 275.

nothing in the whole realm of surgery more gratifying than the successful removal of a meningioma with subsequent perfect functional recovery." He is careful to add that the operation is often attended by great hazard,
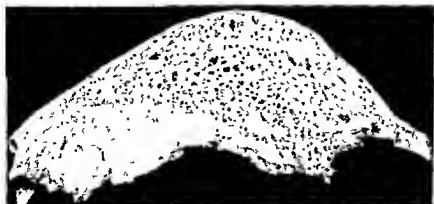
Fig. 424.—Hyperostosis of skull in meningioma.

and often requires two or even three sessions. The frequency in pathological museums of autopsy as compared with surgical specimens of meningioma bears silent testimony to this hazard. It is now realized that the ultimate prognosis is by no means as favorable as has been supposed.

In many instances there is recurrence after an interval of years, due evidently to incomplete removal. Details of such cases will be found in Cushing's fine monograph on the meningiomas. The mere fact that extensive infiltration of bone is so frequent indicates that the tumor is not as benign as might be imagined from the microscopic picture.

Acoustic Nerve Tumors.—A tumor quite distinct from those already considered is that which occurs in the cerebello-pontine angle. It forms a firm, round, lobulated swelling, as a rule is well encapsulated, and lies quite outside the brain (Fig. 425). The tumor frequently compresses and indents the brain stem very markedly and may displace it across the middle line, so that it presents a distinct curve in place of a straight line. It is of the same nature as the multiple neurofibromata of von Reekling-

Fig. 425.—Tumor of the nervus acusticus (cerebello-pontine angle tumor). Marked displacement of the pons and cerebellum.

hausen's disease, and may be associated with the presence of multiple peripheral tumors. In his monograph Harvey Cushing has shown that the tumor is usually situated within the internal auditory meatus which is markedly enlarged. He considers that it arises from undifferentiated cells at the junction of the glial elements with the sheath of Schwann, and that it is essentially a tumor of the sheath of Schwann. On this account the tumor is sometimes called a neurinoma. Others think that it arises from the connective tissue of the perineurium, and is therefore a fibroblastoma, a view which appears the more probable. *Microscopically* the tumor is composed of elongated cells which occur in bundles and even in whorls. The nuclei of adjacent cells may lie side by side, producing a peculiar and characteristic banded or "palisade" appearance. The general arrangement recalls that of the meningioma.

Although these tumors are so well encapsulated and lie completely outside the brain substance, operative treatment used to be attended by an appalling mortality owing to the proximity of the tumor to the brain stem. The method of intracapsular enucleation has almost eliminated the danger, a striking example of what may be affected by a change in technic.

PITUITARY TUMORS

Pituitary tumors are for the most part benign adenomas arising from the anterior lobe of the gland. The epithelial cells of this lobe are of three types: (1) chromophobe cells (50 per cent), with pale-staining non-granular cytoplasm; (2) acidophil or eosinophil cells (40 per cent), with granules which stain red with acid stains such as eosin, or better, acid fuchsin; (3) basophil cells (10 per cent), with granules which stain blue with basic dyes. The acidophil cells apparently govern growth. The basophil cells are perhaps concerned with sexual development, but of this there is no definite proof. The chromophobe cells have no known function, but probably are the parent cells of the other two types. Corresponding to the three types of cells the tumor may be an acidophil, basophil or chromophobe adenoma. The chromophobe adenoma can obviously not give rise to symptoms of glandular over-activity, but may destroy and replace the active cells, thus giving a picture of hypopituitarism. The acidophil and basophil adenomas are marked by symptoms of hyperpituitarism, especially in the earlier stages.

Chromophobe Adenoma.—This is much the commonest form. The tumor, which may vary greatly in size, is spherical and encapsulated. In most cases the cells show a characteristic alveolar grouping, with fibrous septa between the groups (Fig. 426) but they may be arranged diffusely. The cytoplasm is pale and contains no granules. Small nonencapsulated groups of chromophobe cells, sometimes arranged in tubular form, are of common occurrence in the pituitary. They have been called subclinical adenomas but are rather areas of hyperplasia than adenomas.

When endocrine symptoms are present they are those of pituitary insufficiency, similar to the changes produced in an animal when the pituitary is removed; they are the result of compression of the more actively functioning eosinophil and basophil cells. In children the picture is that of Fröhlich's syndrome, a combination of sexual infantilism, excessive adiposity, mental torpor, and a high sugar tolerance. The fat boy fairly bursting from his clothes and ready to sink into slumber at a moment's notice has been drawn for all time in the immortal pages of *Pickwick*. The condition may develop after puberty, in which case the deposits of fat in the breast, hip, and abdominal regions will give the man a distinctly feminine cast of figure. It is of importance to note, however, that the most common cause of hypopituitarism of the Fröhlich type is not chromophobe adenoma of the pituitary but craniopharyngioma. Pressure on the hypothalamus is mainly responsible for the adiposity. If the tumor remains confined to the sella turcica there will only be interference with skeletal and sexual development, but if it breaks through the membranous roof and presses on the tuber cinereum, hypothalamic adiposity will be superadded.

Acidophil Adenoma.—This form, usually called eosinophil adenoma, is

much less common. It is composed of cells filled with red-staining granules (Fig. 427), the cells are large and often multinucleated, and they are arranged diffusely, with complete absence of the alveolar grouping so characteristic of the chromophobe adenoma. The eosinophil cells are concerned with skeletal growth, so that the tumor is associated with the syndrome of overgrowth, i. e., gigantism or acromegaly. The eosinophil adenoma may give rise to the nearest approach to pure hyperpituitarism (skeletal overgrowth, connective-tissue hyperplasia, hypertrichosis, glycosuria, increased metabolic rate), but later in the disease insufficiency symptoms become apparent.

Basophil Adenoma.—This is by far the rarest form of pituitary adenoma. It is composed of basophil cells, and, according to Cushing, may give rise to a striking and specific clinical picture. The chief symptoms are: (1) painful adiposity which is confined to the face, neck and trunk, but spares the limbs; (2) hirsutism; (3) sexual dystrophy, e. g., dysmenorrhea in females, impotence in males; (4) vascular hypertension; (5) peculiar striations of the skin which give the abdominal wall an appearance of pregnancy. This group of symptoms has been called Cushing's syndrome. It now appears probable that the pituitary nodules, which are often remarkably small, are secondary rather than primary in character, the essential lesion being in the adrenal cortex in the form either of an adenoma or diffuse hyperplasia. The importance of this change of outlook from the surgical point of view is self-evident. The really characteristic pituitary lesion is not the adenoma, which is frequently lacking, but a hyaline change in the granular basophil cells, which is a constant finding.

Malignant Adenoma.—Carcinoma of the pituitary is rare. In Cushing's series there were only 3 malignant tumors compared with 159 innocent ones. The tumor destroys the base of the skull, bursts through the roof of the sella, and invades the floor of the third ventricle. In one case which I studied the patient had marked cerebrospinal rhinorrhea; whenever he sat up in bed cerebrospinal fluid dripped steadily from the left nostril, owing to a communication between the cranial and nasal cavities. The cells, which are of the chromophobe type, are grouped in irregular masses and are atypical in size and shape.

Craniopharyngioma.—This tumor, also known as hypophyseal duct tumor, arises from remnants of the primitive duct which extends from Rathke's pouch upward and backward as far as the pars nervosa and along the infundibulum. Normally small masses of squamous epithelium can be found along the pituitary stalk, and as it is from these that the tumor usually arises it follows that it is usually situated above the diaphragma sellae and is known as a suprasellar tumor. It may, however, develop within the sella itself. The tumor is probably more common than the true pituitary adenoma. It is usually an epidermoid carcinoma of squamous type, but basal-cell carcinoma of the adamantinoma type may also occur. The blood supply is poor, and as the tumor increases in size degeneration and cyst formation are very common, so that at operation only a large cyst filled with fluid containing cholesterol crystals may be found. Calcification of the wall of the cyst is of very frequent occurrence, and the demonstration of this on the roentgen-ray film is of the greatest diagnostic value.
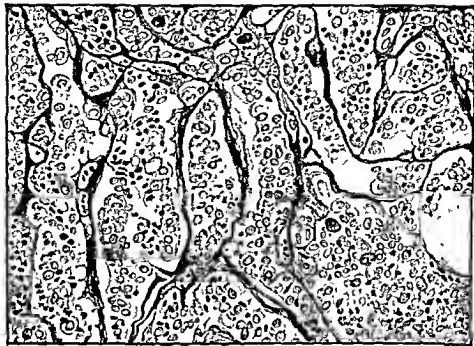
Fig. 426—Chromophobe adenoma of pituitary. The pale cells show a definite alveolar grouping. Four acidophil cells are present. (Author's Textbook of Pathology, Lea & Febiger, Publisher.)
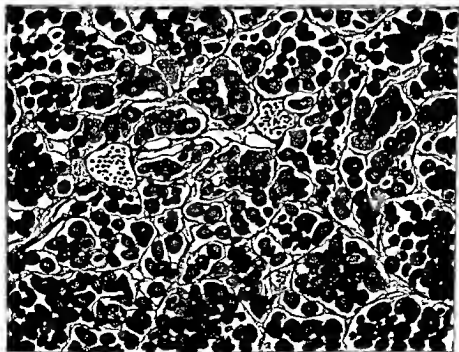
Fig. 427.—Eosinophil (acidophil) adenoma of pituitary. The cytoplasm of the cells is intensely red compared with that of the red blood cells in the capillaries. The arrangement is much more diffuse than in the chromophobe adenoma. (Author's Textbook of Pathology, Lea & Febiger, Publisher.)

The tumor, which may appear at any period of life, but usually under the age of fifteen years, attains a much larger size than the average pituitary adenoma. It does not balloon out the sella like the latter tumor, but flattens it from above downward, and having destroyed the diaphragma erodes the dorsum sellae, at the same time flattening the pituitary so that it may only be recognizable microscopically. It grows upward into the third ventricle, sometimes filling that cavity, and interferes with the circulation of the cerebrospinal fluid so that marked hydrocephalus of the lateral ventricles may develop with widening of the sutures.

The symptoms are a combination of hypopituitarism and the hypothalamic syndrome owing to the pressure of the tumor both upward and downward. Among these symptoms are amenorrhea, failing libido, low basal metabolic rate, loss of hair, stunting of growth, obesity in young
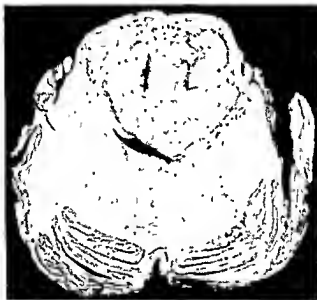
Fig. 478.—Tuberculoma of midbrain.

adults, sleepiness, and polyuria, the last-named differentiating it from adenoma of the pituitary. Suprasellar calcification is a sign of the greatest value.

Neighborhood Symptoms.—These are caused by pressure on neighboring structures. Pressure on the optic nerve causes optic atrophy of the primary type. The most characteristic pressure symptom is bitemporal hemianopia due to compression of the inner fibers of the optic chiasma. There may be pressure on the hypothalamus with production of the hypothalamic syndrome (adiposity, polyuria). This is more likely to be caused by a chromophobe than a chromophil adenoma, as the latter remains confined to the sella long after the development of symptoms of hyperpituitarism. The sella is always expanded by the tumor, and may be markedly ballooned, with absorption of the clinoid processes.

Tuberculoma.—The large solitary tubercle is a peculiar manifestation of tuberculosis in such organs as the brain and liver where the extension of the inflammatory process is allowed to proceed symmetrically, *unhampered by planes of fascia or strands of connective tissue.* Occurring usually in children, it is frequently multiple, and may attain to the size of a walnut. It is most often found in the cerebellum, the cerebrum coming next in frequency. It forms a firm, well-defined, spherical mass *which may readily be mistaken for a true tumor* (Fig. 428), although if softening occurs it may resemble an abscess. Of the three specimens in the University of Manitoba Pathological Museum one is usually taken for a tumor, the *other two for an abscess.*

Gumma.—Gummata usually originate in the meninges and invade the brain secondarily. The tumor is grey or reddish-grey in color, somewhat irregular in outline, and of firm consistence, although necrosis and softening may occur later. Eventually it becomes replaced by fibrous tissue, tell-tale scars remain, and the meninges are adherent to the surface of the brain.

Pseudotumor Cerebri.—Under this name, which is clinical rather than pathological, are included certain cases which present the cardinal symptoms of cerebral tumor, but in which the clinical course disproves the diagnosis. Many pathological lesions may give rise to symptoms which simulate cerebral tumor. Scattered amongst the literature are to be found cases resembling tumor cerebri in which the underlying condition was cerebral syphilis, atypical tuberculous connective tissue changes, meningo-encephalitis, and basal meningitis. In many of the cases there has been an abundant serous exudate in the brain.

A definite entity is the condition known as *chronic serous arachnoiditis.* The clinical picture was described by Quincke in 1893, but we are indebted to Cushing's Clinic for a more exact study of the underlying lesion. The condition may be local or generalized. The generalized form named by Horrax "cisternal arachnoiditis" may simulate cerebellar tumor with great exactness. There is a marked thickening of the arachnoid forming the large posterior cistern over the cerebellum, and also of the basilar cisterns. Histologically the membrane shows a chronic inflammatory thickening of unknown etiology. There is obstruction to the circulation of cerebrospinal fluid, so that the cisterns at the base of the brain become much enlarged and an internal hydrocephalus develops. The neurological findings give the localizing features of a cerebellar lesion simulating tumor, but the wide opening of the basal cisterns by operation has afforded almost complete relief in the majority of cases.

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THE SPINE AND SPINAL CORD

THE INTERVERTEBRAL DISCS

Remarkable advances have been made in recent years in knowledge of the pathology of the intervertebral discs. These advances are entirely due to one man, Schmorl of Dresden, who took up the study of the vertebral column after having given up his active professional work on account of age. In his excellent review of Schmorl's work Beadle remarks that "the intervertebral disc is a living unit whose function is to control the continual and infinitely various cross-currents of tension, torsion, pressure and mechanical shock which interplay with one another as injurious agencies during every moment of life." The bodies of the vertebrae are not separated by joint cavities but by a highly elastic and fluid tissue mass, the *nucleus pulposus*, compressed between the vertebral surfaces like a compressed spring. It is composed of remnants of the notochord of the embryonic spine. Around the nucleus pulposus is a coarse fibrous ring, the *annulus fibrosus*, which corresponds with the fibrous capsule of other joints and which forms the major part of the disc. The articular surface of the bone is covered by a hyaline *cartilaginous plate*. The disc therefore consists of nucleus pulposus, annulus fibrosus and cartilage plate. The surface of the vertebra is perforated by numerous fine holes, so that the spongy bone is exposed. The disc acquires its food supply by diffusion of fluid through these minute channels, as there is no synovial fluid. It is small wonder that the discs show a greater tendency to degeneration with advancing years than any other tissue in the body. The spine, indeed, is the first organ in the body to undergo the degenerative changes of age, being not surpassed in this respect by the intima of the large arteries. In the middle decades well-preserved discs are the exception, not the rule; perhaps this degenerative tendency is associated with the assumption of the erect posture in man.

The nucleus pulposus is the essential part of the disc, and it is it which plays the chief rôle in pathological changes. In youth it presents a very marked elastic turgor, depending on the fluid content of the tissue, but with age this gradually diminishes, and is completely lost in various degenerations. As the nucleus loses its fluidity and becomes desiccated and solid, the disc loses its firmness and becomes fragile and easily torn. Later the whole disc swells and is converted into a sodden mass like lumps of porridge. The spinal curvatures of advancing age are the consequence of degeneration of the discs.

The most frequent lesion is herniation of the nucleus pulposus (Fig. 429A, B), which was present in 38 per cent of 3000 vertebral columns removed by Schmorl at autopsy. It is the combined result of the internal pressure of the nucleus and weakening of the cartilage plate or the verte-

bral body by injury or disease. As the result of tearing of the cartilage plate (as in compression fracture) the turgid nucleus pulposus bulges into the body of the vertebra and may occupy the greater part of it. These common lesions are known as Schmorl's nodes. The vertebra may be weakened by osteoporotic change as in osteomalacia, again allowing prolapse and ballooning of the nucleus. In adolescent kyphosis the primary lesion is in the discs, which are riddled with multiple remains of the notochord; fine tears appear in the cartilage, and as the substance of the nucleus pushes its way out these tears enlarge into wide fissures, so that there are multiple prolapses over the entire spine.

Herniation into the vertebral bodies is not accompanied by symptoms, but if the annulus fibrosus gives way and prolapse takes place into the vertebral canal, pressure symptoms are likely to result. In the past the prolapsed disc has been mistaken for chondroma or fibromyxoma. Extru-

Ant. long. lig.

Post. long. lig.

Nucleus pulposus

Dura

Herniation of nucleus pulposus
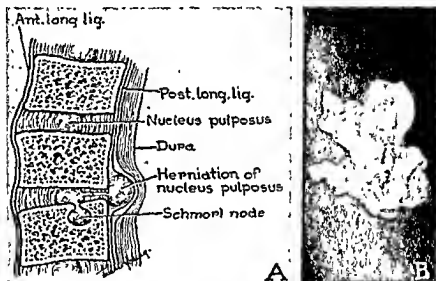
Schmorl node

Fig. 429.—A, Herniated nucleus pulposus and Schmorl node. (Peet and Echols, *Arch. Neurol. and Psychiat.*, **32**, 1934.) B, Herniated disc removed at operation.

sion of the intervertebral disc substance of sufficient degree to cause clinical symptoms occurs, in the vast majority of cases, between the fifth lumbar vertebra and the sacrum or between the fourth and fifth lumbar vertebrae. The extrusion is typically of the lateral part of the disc backwards into the spinal canal and the symptoms are produced by pressure on either the fifth lumbar or first sacral nerve root. A history of trauma as the cause of the extrusion is obtained in about half the cases. Low back pain is the first symptom, made worse by turning or stooping. As the compression of the individual nerve root becomes more established the clinical picture becomes one of severe sciatica. Physical examination now shows anesthesia and muscle weakness corresponding with the distribution of the fifth lumbar or first sacral nerve root to the affected limb. The physical signs are, as a rule, sufficiently clear cut to obviate the necessity of localization by the injection of lipiodol or air into the spinal subarachnoid space.

The rare disc-extrusions in the cervical and thoracic segments of the vertebral column may cause compression of the ventral surface of the spinal cord.

The entire disc becomes thinner with age; this is the chief cause of the loss of height in old people. Calcification of the disc is rare. In tuberculosis (Pott's disease) the disc disappears early; this might be regarded as Nature's method of obtaining bony fusion. In osteomyelitis of the spine the disc is rapidly destroyed. In secondary carcinoma of the vertebrae there may be some prolapse into the vertebral body, but the disc itself is remarkably resistant to invasion, a very useful radiological distinguishing feature between tuberculosis and carcinoma of the spine. In spondylitis deformans the primary lesion seems to be a fibrous degeneration of the discs, the bony ankylosis and formation of osteophytes being a secondary defense mechanism for bracing the spine.

SPINA BIFIDA

Spina bifida is a congenital defect due to failure of the neural arches to close, and accompanied by a protrusion of the contents of the spinal canal. As normally the lower part of the canal is the last to close, spina bifida is commonest in the lumbo-sacral region, although any part of the spine may be affected. As a rule about five or six vertebrae are involved, sometimes only one, very rarely the entire column. The condition is fairly common, occurring about once in every 1000 births.

The contents of the sac may be of three varieties: (1) a meningocele, (2) a meningomyelocele, and (3) a syringomyelocele.

Meningocele.—This usually occurs in the sacral region. It consists of a sac composed of the dura and arachnoid and is filled with cerebrospinal fluid, but contains no nervous structures. At birth it is usually not larger than a hen's egg, but it may rapidly increase in size. It frequently becomes pedunculated. The skin is usually normal at first, but becomes thinned as the cyst increases in size, and may finally give way.

Meningomyelocele.—In this condition, which is the commonest form of spina bifida, and which usually occurs in the lumbar region, the sac contains the spinal cord or the cauda equina in addition to the cerebrospinal fluid. The cord may pass straight back into the sac and end by becoming attached to its wall. If the defect is higher up the cord may enter and leave the sac. The cord and the nerves are usually flattened and frequently attached to the wall of the sac, producing a dimple known as the umbilicus. The sac is sessile, and the overlying skin is so thin that, by means of illumination, it may serve to distinguish the condition from a meningocele. A meningomyelocele is naturally a much more serious condition than a simple meningocele.

Syringomyelocele.—This is a rare form of spina bifida in which there is a great distension of the central canal with consequent thinning of the nervous tissue of the cord. The wall of the sac is therefore actually lined by the thinned wall of the canal. The condition is apt to be mistaken for a meningocele, because at first sight no nerves are evident in the sac. Closer inspection will disclose the nerves incorporated in the wall of the sac, that is to say in the distended cord.

The various forms of spina bifida are frequently accompanied by complications. The most significant of these is congenital hydrocephalus, for it suggests a causal relationship between the two conditions. Other accompaniments are paralysis of the bladder and rectum, weakness in the muscles of the legs leading to club-foot, trophic ulcers, etc., due to pressure on the nerve centers. When the lesion is in the sacral region there may be no nervous disturbances.

The *prognosis* is bad. Early death is the best termination. Not many cases live beyond the age of four or five. Death is usually due to rupture of the sac or the development of septic meningitis, but occasionally it is due to hydrocephalus.

Spina Bifida Occulta.—In this form of spina bifida the bony defect is not accompanied by any protrusion of the contents of the spinal canal. It follows that it is neither so easily recognized nor so liable to produce symptoms.

Fig. 430.—Pilonidal cyst containing an abundance of hair.

Its presence is usually revealed by the character of the skin covering the bony defect, for this is rough and wrinkled and adorned with a patch of hair which may occasionally resemble a small tail. The opening in the bone can usually be felt, or it may be best revealed by means of the X-rays.

Small tumors, of which the commonest are lipomata and dermoids, may occur either inside or outside the canal. In the latter case they project under the skin. They are developmental in origin, and are due to the growth of embryonal cells which continue their activity after the formation of the defect.

There may be no symptoms, or there may be paralysis of the legs and the sphincters, club-foot, the development of trophic ulcers, and other symptoms difficult of explanation until the spina bifida is discovered. The symptoms are usually due to a tough cord of connective tissue stretching from the skin through the vertebral defect and attached to the termination of the cord, on which it exerts traction with the production of nervous

symptoms. The traction is due to the fact that the vertebral column grows at a faster rate than the connecting strand, and as the chief period of growth is between the ninth and fifteenth years, it is at this time that the symptoms are most likely to appear.

Pilonidal Sinus and Cyst.—Pilonidal means a nest of hair. The lesion arises in the middle line in relation to the skin dimple at the tip of the coccyx, and is due to an error in development. The dimple marks the site of attachment of the primitive neural canal. A sinus tract may extend from the dimple deep into the tissues, sometimes as far as the vertebral bodies. The sinus is lined by squamous epithelium from which hair may be growing (Fig. 430). Healing will not take place unless the entire epithelial wall is excised. The depth to which the tract may extend explains the frequent recurrence which is so characteristic. Closure of the external opening leads to the formation of a cyst, and, as infection is common owing to the site, an abscess or discharging sinus may result. The cyst may remain quiescent till the ages of fifteen to thirty, when it may become infected. Although the position of the lesion suggests an origin from vestiges of the neural canal, the squamous lining is in favor of an ectodermal origin, possibly from excessive traction on the skin caused by retrogression of the tail bud.

CONGENITAL SACRAL TUMORS

Although not related in any way to spina bifida, certain peculiar sacral tumors may be considered here, as they also are congenital in origin. These tumors may be divided into three groups: dermoid cysts, sacral cysts, and coccygeal cysts.

Dermoid cysts occur in the middle line over the sacrum, and usually contain the characteristic sebaceous material, hair, and teeth. Instead of a typical dermoid cyst there may, in rare cases, be anything from a lower limb up to a more or less fully formed fetus. The simpler cysts are formed by the induction of epithelium in the closure of the vertebral groove, but the more complex masses are supposed to originate from the formation of two embryonic areas in a single developing blastodermic vesicle, the one giving rise to the normal individual, the other to the parasitic fetus.

Sacral cysts are cystic, sessile masses containing serous fluid and lined by endothelium. Their exact origin is not certain, but it has been suggested that they represent a sacral meningocele which has been cut off by the continued growth of the vertebral arches.

Coccygeal cysts are placed laterally, thus being distinguished from the two former varieties. Moreover they are situated deeply among the gluteal muscles. They have been thought to arise from the postanal gut, that is to say the neurenteric canal.

FRACTURES OF THE SPINE

Fracture of the spine is of special interest in view of the possibility of injury to the cord. The spines, the laminae, or the transverse processes may be fractured, but two varieties of fracture deserve special mention, namely compression fracture of the bodies of the vertebrae and fracture-dislocation.

In *compression fracture* of the bodies there is crushing of the bodies of one or more vertebrae owing to the patient falling from a height and landing on his buttocks or his feet. As there is no dislocation there is very little deformity, and usually no laceration of the cord. The bodies being crushed in, there is some projection of the spines.

In *fracture-dislocation* there is a complete bilateral dislocation of the articular processes together with an oblique fracture downwards and forwards of one or more of the vertebrae. The effect on the cord is instantaneous and disastrous, for the upper fragment moves forwards and downwards, nipping the cord and crushing it irretrievably (Fig. 431).
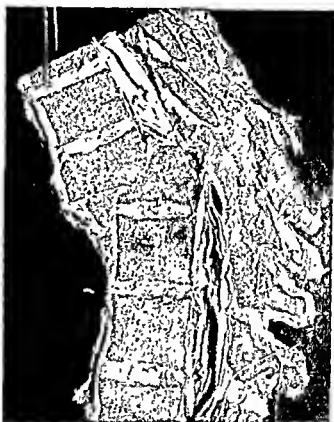
Fig. 431.—Fracture-dislocation of spine with severance of cord.

Pott's Disease of the Spine.—As this is a form of tuberculosis of bone, it is discussed in connection with that condition on page 684.

OSTEOMYELITIS OF THE SPINE

Acute pyogenic inflammation of the vertebrae is commonest, as in the case of other bones, between the ages of 5 and 15, that is to say while the bone is still growing and vascular. Staphylococcus aureus is the chief causal germ.

The inflammation is commoner in the processes than in the bodies of the vertebrae (Fig. 432), thus differing from tuberculosis. When it begins in the arches the pus spreads backwards, when it begins in the bodies it spreads forwards, and, following the example of tuberculosis, may give rise to retropharyngeal, mediastinal, and psoas abscesses. An extradural abscess may form which presses on the cord. Death results from septic meningitis.

Typhoid Spine.—During convalescence from typhoid fever, and occasionally during the course of the disease, an inflammation of the lower part of the spine may develop, associated with great pain and tenderness. As the disease is not fatal there have been no opportunities for post-mortem observations, but X-ray studies leave no room for doubt that the condition is a superficial osteomyelitis, unaccompanied except in rare cases by

suppuration, and followed by new bone formation. X-ray pictures show roughening of the adjacent surfaces of the vertebrae; the intervertebral space becomes narrowed and finally obliterated: osteophytic outgrowths develop at a later date. In tuberculosis, on the other hand, new formation of bone is conspicuously absent.

SYPHILIS OF THE SPINE

Gummatous formation in the vertebrae may closely simulate Pott's disease. It is most common in the cervical region, the deformity is not marked because the destruction of the vertebral bodies is not extreme, there is no abscess formation, other signs of syphilis are present, the onset is more sudden and the progress more rapid than in tuberculosis, and the Wassermann reaction is positive.

TUMORS OF THE VERTEBRAE

The usual tumors of bone may affect the vertebral column, but the only ones which call for special mention are sarcoma, giant-cell tumor, chordoma, myeloma, and secondary carcinoma. Tumors of the vertebrae are usually situated in the bodies.

Sarcoma of the spine is usually primary, but may be secondary. It causes pressure on the cord and may readily be mistaken for Pott's disease. The sacrum is the most common site, and there it may cause severe sciatica.

Fig 432.—Osteomyelitis of the spine. Numerous osteophyte processes project from the bodies of the vertebrae.

Giant-cell tumor of the vertebrae is a rare condition, but nevertheless important. It is apt to be mistaken for sarcoma or secondary carcinoma and therefore considered inoperable. In reality it is quite amenable to treatment, even partial removal sometimes resulting in recovery.

Multiple myelomata, when they do occur, are usually found in the sternum as well as in the spinal column, the cranium, and the long bones. Bence-Jones protein is present in the urine in 50 per cent of the cases.

Chordoma is a rare tumor which occurs at the ends of the vertebral column, and arises from remnants of the notochord. At the upper end of the spine it is found at the base of the skull between the foramen magnum and the pituitary fossa; at the lower end it occurs in the sacrococcygeal region. It is a malignant tumor, but not highly so, and only in the end stages does it form metastases. It is elastic in consistence, and presents areas of translucent chordal tissue interspersed with patches of hemorrhage. *Microscopically* it consists of characteristic, very large, clear, vacuolated cells without any intercellular substance. The cells are distended with mucinous material. (Fig. 433.)

Carcinoma secondary to malignant disease in such glands as the breast and the prostate is common. The bodies of the vertebrae are destroyed, and a deformity suggesting that of Pott's disease may possibly be produced.

Pressure symptoms amounting to complete paraplegia may develop with startling rapidity. Although the vertebrae may be completely replaced by carcinoma, the intervertebral discs escape, in this way differing sharply from tuberculosis (Fig. 434).

Fig. 433.—*Chordoma showing mucin-filled cells.* × 500.
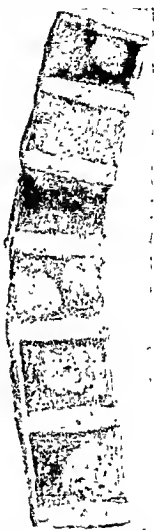
Fig. 434.—*Secondary carcinoma of spine, discs uninvolved.*

INJURIES OF THE SPINAL CORD

The spinal cord may be injured as the result of fracture of the spine, the most common cause; or from bullet or stab wounds; or from mere overstretching of the cord owing to acute flexion of the spine from a blow. The laceration of the cord may be complete, in which case there is immediate paralysis, both sensory and motor, of the entire body below the lesion. Or it may be partial, the varying symptoms depending on the site of the lesion.

Hemorrhage is a very constant accompaniment of spinal injuries. This hemorrhage may be extramedullary or intramedullary.

Extramedullary hemorrhage often gives rise to no symptoms of pressure on the cord, but in some cases there may be indications of pressure

on the cauda equina, owing to the blood gravitating to the bottom of the arachnoid sac and accumulating there in sufficient amount to exert pressure. In the cases where symptoms of cord pressure at the site of the hemorrhage develop, the symptoms are at first irritative in the form of muscular twitchings and root pains and only later paralytic. Moreover the onset of the symptoms is characteristically gradual. Blood in large amount is present in the spinal fluid.

Intramedullary hemorrhage or hematomyelia is always associated with more or less laceration of the cord. The hemorrhage, usually in the cervical region, is generally confined to the grey matter, but it may spread up and down for a considerable distance, so that the resulting paralysis may be correspondingly widespread. The symptoms are at once paralytic without any preliminary period of irritation. Moreover the onset is most abrupt. There may be no blood in the spinal fluid.

SPINAL CORD TUMORS

Tumors of the spinal cord are of more frequent occurrence than is commonly supposed; most of them are missed. The majority develop slowly, especially those of the extramedullary variety. The rapid development of symptoms as a rule indicates that the growth is a malignant one within the cord itself.

Although the cord is much compressed, generally from the side, it is remarkable how few pressure changes develop. It is for this reason that removal of these tumors is often attended with such satisfactory results. In some cases, however, there may be myelitis, hemorrhage and degeneration.

As Frazier remarks, there are three cycles in the life history of any spinal tumor. The first or root cycle is the longest, and the symptoms are unilateral in the early stage; there is first irritation and then compression of the nerve roots. The second cycle is characterized by the Brown-Séquard syndrome, with paralysis of motion and deep sensation on the side of the tumor, loss of pain and temperature sense on the opposite side. The syndrome is present in extramedullary but not intramedullary growths. The third cycle is one of paralysis of the organic reflexes (bladder and rectum) and the deep reflexes, together with vasomotor and trophic disturbances.

Tumors affecting the cord may be: (1) extramedullary, (2) intramedullary.

Extramedullary Tumors.—These tumors seldom invade the cord, but give rise to irritation and compression of the nerve roots. There may be root symptoms long before there is any sign of pressure on the cord; sometimes the interval may be as long as several years. They are usually situated on the lateral or postero-lateral aspect of the cord, so that the anterior roots escape, and there may be no root symptoms.

The tumor as a rule grows very slowly, and although it may exert great pressure degenerative changes are sometimes almost entirely lacking. In other cases there may be considerable softening of the cord, but this is due to interference with the circulation rather than to direct pressure.

The tumor is usually oval, with the long axis in the direction of the cord, but it seldom attains to a size larger than 2–5 cm. in length. A striking feature when the laminae are removed is the absence of pulsation in the

tumor, whereas the cord above and below may show normal pulsation. It is common to find collections of cerebrospinal fluid above the tumor, and very little fluid may be obtainable by lumbar puncture.

The tumor may be extradural or intradural.

Extradural tumors arise from the outer surface of the dura, and are much less common than the intradural variety. The interval between the root symptoms and those of cord compression may be very long, because the tumor is free to grow in a longitudinal manner. These tumors are often *sarcomatous*, and may invade the vertebral column. Hydatid cysts have been found in this position.

Intradural tumors form the commonest variety of spinal cord tumors. They are by far the most suitable group for operation, being usually well encapsulated and easily removed. Two of the most favorable for operation are the *meningioma* and the *fibroma*. Both are firm, encapsulated, and show no tendency to invade the cord (Fig. 435). Intradural tumors have frequently been reported as sarcoma, but even such tumors show a curious reluctance to invade the cord, although they may seriously compress it.

Intramedullary Tumors.—These constituted 11 per cent of Frazier's cases. The sequence of symptoms is often the opposite of that seen in extramedullary tumors, for the first or root period may be entirely lacking, and the progress of the disease is much more rapid. The tumor is generally limited to the cord, and seldom invades the meninges or the spine. It extends up and down rather than horizontally, so that the overlying dura may appear normal. The characteristic absence of pulsation indicates the site of the lesion.

The *glioma* is the common intramedullary tumor. It is a diffuse growth which may infiltrate large segments of the cord. Indeed Mallory describes a case in which a glioma originating in the lower part of the cord spread upwards till it reached and passed through the foramen magnum, and continued its course over the surface of the brain. A glioma may, however, be circumscribed and even encapsulated. The cyst formation so often seen in the brain is rarely met with in the cord.

Fig. 435.—Intradural tumor of cord.

Sarcoma of the cord is a rare condition. A solitary *tubercle* of the cord will produce all the symptoms of a neoplasm. *Gummata* occasionally occur in the cord, but are much commoner in the meninges.

Cerebrospinal fluid changes are sometimes of great diagnostic value, not so much for determining the site and nature of the tumor as for detecting the presence of some process causing compression. The "compression syndrome" when fully fledged consists of the following: (1) massive spontaneous coagulation of the fluid due to an excess of fibrinogen; (2) xanthochromia or yellow coloration of the fluid; (3) marked increase in the protein; and (4) no corresponding increase in the cells, although if menin-

geal irritation is present there may be some lymphocytosis. The fully developed Froin syndrome is seldom seen, but the protein increase without a corresponding lymphocytosis is of common occurrence. It must be remembered, however, that any process which divides the spinal canal into a large upper compartment in communication with the cranial cavity and a small lower cul-de-sac will give rise to this condition. I have seen a case diagnosed from this test as one of spinal cord tumor which turned out at autopsy to be an example of Pott's disease with no deformity of the spine. On the other hand a tumor of the cord or the meninges which is not sufficiently large to obstruct the canal will produce no effect on the spinal fluid. With these exceptions the test is a very useful confirmatory one.

The Froin syndrome merely suggests the presence of a spinal cord tumor. It does not serve to localize it. This can be done by the injection of lipiodol into the spinal canal, a method introduced by Sicard, in 1921. This oil holds sufficient iodine in suspension to give a heavy shadow in the X-ray, so that the level of the tumor may be indicated with great exactness.

Ayer has shown that when a double puncture is employed (cisternal and lumbar), the pressure is always greater in the higher puncture, provided that there is a complete block between the two points of puncture. A much simpler method is that introduced by Queckenstedt in 1916, who showed that the pressure in the lumbar canal rose following compression of both jugular veins when there was no obstruction in the spinal canal, but that the pressure did not change when obstruction was present.

Specific tumor cells can sometimes be found in the fluid. This is particularly true of diffuse sarcomatosis of the meninges.

Circumscribed Serous Meningitis.—Operations on the spinal cord have revealed a condition which may so closely simulate a spinal cord tumor as to deceive the very elect. A cyst-like space of varying size, containing clear cerebrospinal fluid, and limited by the arachnoid, is seen to be pressing on the cord which has a shrunken appearance. The fluid is under marked tension. The condition appears to commence in the lower part of the cord, and to spread up as far as the middorsal region. The exact cause is unknown, although syphilis, trauma, and the other factors usually invoked in obscure neurological conditions, have all been cited. It may be that a mild meningitis has given rise to adhesions which, by cutting off a portion of the subarachnoid space, are responsible for the condition. The symptoms are those of an extramedullary tumor. The condition is probably related to the chronic serous arachnoiditis which may closely simulate cerebral tumor.

INJURY AND REPAIR OF NERVES

When a peripheral nerve is divided the distal part of each fiber undergoes the changes known as *Wallerian degeneration*. The axis cylinder becomes fibrillated and disintegrates, the medullary sheath breaks up into droplets of myelin, and the cells of the sheath of Schwann are converted into phagocytes which remove the remnants of the medullary sheath and axis cylinder. Similar changes occur in the proximal part up to the first node of Ranvier.

The first evidence of repair is proliferation of the Schwann cells at the

divided ends, and their arrangement in the form of a tube which acts as a channel along which new axis cylinders can grow. It used to be thought that the Schwann cells of the peripheral portion could lay down fibrils which later joined up with the central portion, but it is now believed more probable that new fibers grow out from the divided proximal end and pass along the track formed by the Schwann cells, although it is difficult to explain on this theory the speedy return of function which sometimes occurs.

In the course of a few days the axis cylinder grows out as a bulbous process in search of the missing distal end. If, however, the space between the two ends is more than an inch the attempt at union fails, and the same is true if the ends are separated by scar tissue. Transplantation of a nerve between the divided ends merely serves as a bridge across the gap along which the new fibrils can travel. When the bulbous end of the axis cylinder reaches the distal portion it puts out fine fibrils which grow down the tubular sheath formed by the proliferated Schwann cells. These fibrils reestablish the continuity of the pathway and become clothed again, with the assistance of the Schwann cells, by a medullary sheath. If the distance is too great to be bridged or if the part supplied by the nerve has been amputated, the axis cylinders may coil up so as to form a nodule capped by fibrous tissue. Such a mass at the end of a nerve, composed of nervous and fibrous tissue, is called an *amputation neuroma* (stump neuroma). Some degree of sensation may reappear fairly quickly, but complete restoration of function, even when the cut ends are brought into accurate apposition, seldom occurs in less than three or four months.

TUMORS OF NERVES

There is no more confused subject in the whole realm of tumor pathology than that of tumors of nerves. Newer staining methods and increased knowledge of nerve histology should have brought better understanding, but they have served rather to make confusion more confounded. As Foot remarks in a comprehensive review which should be consulted: "Things that once seemed simple have become complex, and one is faced with controversies that seem impossible of solution through the means at hand, questions that never troubled the older pathologists, because they never suspected their existence." One of the fundamental difficulties is that there is difference of opinion among histologists as to the essential structure of normal nerves. "The histology of the nerve trunk seems quite simple and well understood if one reads but a single authoritative paper on the subject, but should one read several it will take on more and more complexity." (Foot.)

The tumors with which the surgeon is concerned are those arising from the nerve sheath, and it is these which have been the subject of a lively controversy which is reflected in the nomenclature. The first to study them was Virchow (1863), who applied the name neuroma, a tumor of nerve. Most modern workers, following the lead of Mallory and Penfield, regard them as fibroblastomas, innocent or malignant, arising from the connective tissue sheath (*perineurium*) of nerves, so that they have been called perineurial fibroblastomas. The French school, on the other hand, of whom Masson is the chief exponent, believe that they arise from the

cells of the sheath of Schwann and therefore call them Schwannomas. Stout proposes the term neurilemmoma as noncommittal and including both Schwann cells and endoneurium.

No matter which view is adopted, from a practical standpoint it can be said that tumors arising from nerve sheaths present a definite structure not found in fibroblastomas elsewhere. Although different groups of these tumors differ considerably from one another they possess the following common features: long, slender, wire-like fibers with elongated nuclei which have a tendency to be arranged in parallel or palisade fashion; in
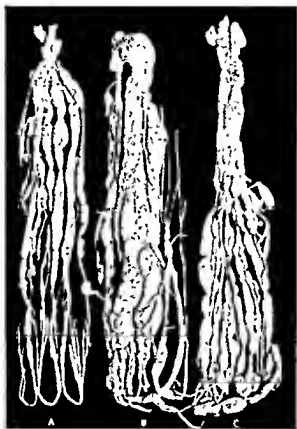
Fig. 436.—Multiple neurofibromata of the peripheral nerves. *A*, Nerves of the right arm; *B*, the left sciatic with its branches; *C*, the left anterior crural with its branches (Prudden's case, from Ewing's Neoplastic Diseases.)

addition to the palisading, which always suggests a nerve sheath origin, the nuclei may be grouped in eddies and streams. The more benign the tumor, the more pronounced are these features. The palisading is perhaps best seen in the acoustic nerve tumor, while the whorls are characteristic of meningioma, a lesion which has much in common with tumors of cranial and peripheral nerves. Penfield and Young have recorded a case presenting multiple neurofibromata, acoustic nerve tumor, similar tumors on several of the other cranial nerves, and multiple meningiomas. The whorls, palisading, etc., tend to be lost in the more malignant forms.

Perineurial Fibroma.—This is also called perineurial fibroblastoma, benign solitary tumor, and *neurinoma*. The latter term was used originally by those who believe that the tumor is a Schwannoma, arising from the cells of the sheath of Schwann. It is a benign tumor which forms a round or fusiform firm white mass on the course of one of the larger nerves. It is attached to the sheath of the nerve, but the nerve fibers are not incorporated in the tumor. *Microscopically* it is composed of long slender cells, the elongated nuclei of which are arranged in palisades or show whorls and eddies. This structure is identical with that of the acoustic nerve tumor, which also is a perineurial fibroma.

It has been suggested that at least some cases of *Dupuytren's contraction* are of neoplastic nature, possibly related to neurinoma. The lesion in the palm of the hand consists of fusiform cells which may show
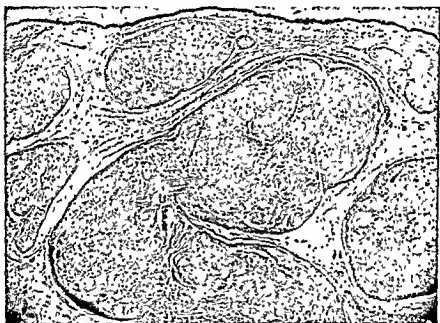
Fig. 437.—Multiple neurofibromata in the skin. (Von Recklinghausen's disease.) × 8.

the suggestive arrangement in whorls and eddies, although in other places there may be dense fibrosis. The steadily progressive character of the lesion would support this idea.

Neurofibroma and Neurofibromatosis of Von Recklinghausen.—This tumor may be single or multiple. Like the preceding form it occurs in definite relation to a nerve or nerves. Both fibrous tissue and schwannian tissue seem to be combined in this lesion. Virchow in his original description describes the growth as "complex organoid tumors," a definition that fits neurofibroma perfectly. Foot remarks that the tumors of this group may contain nerves with sheaths, nerves without sheaths, sheaths without nerves (containing Schwann cells), and about all this there are masses of fibrous tissue.

In *multiple neurofibromata* or von Recklinghausen's disease, a familial condition, there are large numbers of tumors, sometimes several hun-

dreds of them, growing from the fine cutaneous nerves. Similar tumors may occur on the cranial nerves, and on the deeper and visceral nerves (Fig. 436). The deeper growths are prone to sarcomatous change, and this is a frequent cause of death. Sometimes there is a diffuse neurofibromatosis of the nerves of the head and neck, a condition termed *plexiform neuroma*, most often found in the distribution of the fifth cranial and upper cervical nerves. In the common cutaneous form (Fig. 437) soft nodules in the skin (*molluscum fibrosum*) are distributed over the entire body. The skin is often pigmented in patches, a feature of interest in relation to the nervous origin of pigmented nevi. Peculiar soft overgrowths of connective tissue may occur, causing great enlargement of a limb, a form of elephantiasis. The condition appears to be more of a general overgrowth of nerve tissue than a simple tumor.

The *microscopic picture* is much more mixed than in the case of perineurial fibroblastoma. The characteristic tissue has a tangled or reticular structure, which suggests a malformation rather than a neoplasm; this tissue does not show palisading or whorls. Superimposed on this reticular tissue is a varying amount of tissue of the perineurial type showing palisades and whorls. With special stains nerve fibrils can be seen passing through the mass; this never occurs in a perineurial fibroma. It would appear that in von Recklinghausen's disease all the elements composing the nerve are involved in some degree.

Neurogenic Sarcoma.—Ewing and other members of the Memorial Hospital group (Quick and Cutler, Stewart and Copeland) believe that the great majority of what have formerly been regarded as fibrosarcomas of the soft parts are derived from nerve sheaths and should be called neurogenic sarcomas. The cell of origin is supposed to be the Schwann cell. As a rule no connection with a nerve can be demonstrated. They form single slowly-growing tumors, usually in the subcutaneous and intermuscular tissues of the arm and leg. The commonest location is the thigh. The writer has seen one specimen in the wall of the stomach. When the tumor is first removed it may not be possible to say from the histological picture that it is malignant, but it is safe to say that it will recur, this time in a more malignant form, and with a marked tendency to invasion. The new tumor may not be a true recurrence but rather a fresh tumor arising from cells in the vicinity. Neurogenic sarcoma is radioresistant, but low-grade tumors may vanish with prolonged treatment. *Microscopically*, the tumor consists of elongated cells or fibers arranged in interlacing bundles and showing a "curly" arrangement, in contrast to the parallel disposition of the fibers of a pure fibroma (Fig. 438).

Fig. 438.—Neurogenic sarcoma. × 150.

Nerve Nevus.—Nevus and malignant melanoma of the skin are most probably derived from sensory endorgans, so that they may be classed as nerve tumors. The neurogenic origin of pigmented tumors is of interest in view of the frequent occurrence of patches of pigmentation in multiple neurofibromatosis.

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CHAPTER XXX

DISEASES OF BONES

GENERAL CONSIDERATIONS

Without attempting to give a detailed description of the structure of bone, a few anatomical points may be recalled with advantage. Bone is merely a form of connective tissue in which lime salts are deposited in the ground substance. The connective tissue is collected into strands or lamellae between which there may be interspaces occupied by the marrow. Bone is described as compact or cancellous, depending on the amount of interspaces which it possesses.

A long bone consists of a shaft or diaphysis and two extremities or epiphyses, separated from the shaft by the epiphyseal cartilage and themselves covered by hyaline articular cartilage. That part of the shaft which abuts on the epiphyseal cartilage is of special importance in pathology and is called the metaphysis. It, like the epiphysis, consists of cancellous bone, the interstices of which are filled with red marrow. The epiphyseal cartilages at the knee are more active and become ossified later than those at the hip and ankle. In the upper limb it is the cartilages at the shoulder and wrist which are especially active. It may be noted here that inflammatory processes in the leg are common at the knee, in the arm they are commoner at the shoulder and wrist.

New Bone Formation.—The periosteum constitutes the external covering of the bone, loosely attached to it except in the epiphyseal region through the medium of a delicate areolar tissue. In the interstices of this areolar tissue may be seen large cells whose function is osteogenie. These are the osteoblasts. They are abundant in the growing bone, but scanty in the adult. These cells have always been regarded as belonging to the periosteum, and that layer has been considered to be essentially osteogenie in function. Histologists describe the periosteum as consisting of two layers, an outer or fibrous layer and a deep or osteogenie layer.

For 200 years, as Ham points out in an excellent review of the subject, there has been difference of opinion as to whether new bone is formed by periosteum or by bone cells. Macewen (1912) was the principal advocate of the view that new bone is formed only from preexisting bone, not periosteum. As often happens, there is truth on both sides. Both periosteum and bone are composed of two types of cells with quite different potentialities, *i. e.*, fibroblasts and osteoblasts. Adult bone cells do not proliferate. Osteogenie cells line the Haversian canals and the interior of the medullary canal, but identical cells occur in the deep layer of the periosteum. The periosteum consists of an outer fibrous layer and an inner osteogenie layer. When stripped off it is apt to split, the deep layer adhering to the bone. If, however, it be removed carefully to avoid this splitting, it is capable of forming bone.

A bone-forming cell in the presence of an abundant blood supply tends to become an osteoblast; in the absence of such a blood supply it tends to become a chondroblast. The matrix contains fibers and a very high mineral content (calcium phosphate and calcium carbonate). Cells are needed for the deposition of calcium, but the action is indirect, not direct. Young bone cells and adult cartilage cells produce an enzyme, phosphatase, which hydrolyzes phosphoric esters and liberates free phosphate ions with resulting calcification. Two factors are therefore necessary for successful calcification: (1) bone cells which produce a matrix with a ground substance having an affinity for calcium salts, and (2) an enzyme which causes a local increase of free phosphate ions, and thus enhances the precipitation of calcium from adjacent tissue fluids.

New bone formation is an important feature in many pathological conditions. The repair of a fracture is brought about by the rapid proliferation of the osteoblasts, which together with the new capillaries form a granulation tissue which is converted into osteoid tissue and then into bone. This repair is not dependent on the periosteum. Indeed Macewen has shown that if a fracture is produced in a bone from which the periosteum has first been removed the formation of new bone (callus) will be more abundant than under ordinary conditions. In osteomyelitis the involucrum or new case is formed by the proliferating fibroblasts. It is true that here, as in the bone production which follows the subperiosteal hemorrhage of infantile scurvy, the new bone may be formed under the periosteum as well as on the surface of the shaft, but this is to be explained by the enormous proliferation which the osteoblasts undergo in the early stages of the irritation so that when separation of the periosteum occurs many osteoblasts are carried up with it. As a matter of fact subperiosteal resection is most likely to prove successful and to be followed by a complete restoration of bone in cases where previous inflammation has led to marked proliferation of the osteoblasts and commencing new bone formation.

Although recent work has deprived the periosteum of some of its osteogenic function, it nevertheless remains a structure of the greatest importance, for the bone is dependent on the periosteum for the greater part of its nourishment. If the periosteum is stripped from the shaft, or raised from it by an effusion, the underlying bone will die. If no bacteria are present, as in the case of infantile scurvy, there may be no clinical evidence of the occurrence of necrosis, for the necrosed bone is quietly absorbed and replaced by new bone. If such necrosis should occur in the presence of sepsis, however, the result will be very different—an osteomyelitis of indefinite duration and the formation of a sequestrum.

The periosteum is easily separated from the underlying bone, so that inflammation may readily spread along the space between the two structures. When the periosteum reaches the epiphyseal cartilage the outer layer is continued on over the epiphysis, but the inner becomes fused with the epiphyseal cartilage. Pus under the periosteum, therefore, has difficulty in reaching the epiphysis and the corresponding joint.

Blood Supply.—This is of great importance. The outer layers of a long bone are nourished by the periosteum, the inner layer by the medulla. The intervening compact bone requires a special arrangement. Blood vessels

run longitudinally through the bone in a series of channels called the Haversian canals, around which the bony lamellae are grouped. Another series of vessels passes from the periosteum into the interior of the bone along Volkmann's canals. The nutrient artery enters the bone about the middle of the shaft and immediately divides into two branches, one of which passes in each direction and terminates at the metaphysis in abrupt hair-pin bends. In this region we may expect the blood stream to be at its slowest; and it is here that organisms will be most likely to fall out of the stream. The epiphysis is supplied from vessels which anastomose around the joint from three sets of vessels, the diaphyseal, the metaphyseal and the epiphyseal, and thus epiphyseal vessels communicate with those in the metaphysis.

Absorption of Bone.—Bone is not a static and unchanging structure. It responds with great readiness to influences which play upon it. This response may take the form of deposition or absorption of calcium. The great regulator of calcium metabolism is the *secretion of the parathyroid glands*. Injection of parathyroid extract is followed by a marked increase in the calcium content of the blood (hypercalcemia), and the excess of calcium is excreted in the urine. This calcium is taken from the bones, and these may show an extreme degree of decalcification and rarefaction. A similar result is produced by tumors of the parathyroids. This primary decalcification is known as *halisteresis*. At the same time there is fibrous replacement of the bone structures, and giant-cell formations may occur. *Vitamin D* also plays a part, possibly through the intermediary of the parathyroids, and that hypervitaminosis (D) may produce similar bony changes to hyperparathyroidism.

The removal of calcium from the bones is influenced by local as well as general factors. The local factors are vascular absorption and the action of osteoclasts.

Vascular absorption plays a very important part in the removal of bone. The bone lamellae are arranged concentrically around the blood vessels which run longitudinally in the Haversian canals and transversely in Volkmann's canals. Dilatation of these vessels as the result of inflammation is followed by absorption of the surrounding bone, producing a condition of *rarefaction or osteoporosis*. The mechanism of absorption seems to be a local change in the hydrogen ion concentration. Inflammation is accompanied by a local increase of carbon dioxide, and this increases the solubility of the calcium which is accordingly removed from the immediate neighborhood. It is evident that the greater the vascularization, the more marked will the rarefaction be. Dead bone cannot be removed by vascular absorption. The general statement is true that bone undergoes decalcification if the blood supply is increased, and increased calcification if the blood supply is diminished. Pathological calcification is seen in any mesenchymatous tissue of low metabolism when the vascularity is further reduced by fibrosis due to injury or infection.

Osteoclasts also play a part in the local removal of bone. It is by them alone that dead bone can be removed. The osteoclast is a large cell, often multinucleated, with acidophilic cytoplasm. It probably does not produce decalcification directly, but serves to remove small particles of bone which

have already lost their calcium. For this purpose foreign body giant cells are often formed from the osteoclasts.

There may be too little bone either because bone resorption is too great (osteitis fibrosa) or because there is too little deposition of bone. The latter may be due to failure of the osteoblasts to lay down an organic matrix (osteoporosis) or to failure in deposition of calcium in the matrix (osteomalacia). Osteoporosis often occurs from disuse, as the stresses and strains of action seem to stimulate the fibroblasts. In old age osteoblastic activity flags, giving senile osteoporosis. Osteoporosis is often seen in women after the menopause, at a time when the body is no longer liable to be called upon to form bone for babies; this may be called post-menopausal osteoporosis.

The *effect of metals on bone* is of importance, because metal screws in bone tend to become loose owing to bone absorption. Venable has shown that this is due to electrolytic action. When two different metals are inserted either in soft tissues or bone an electric current is generated owing to the creation of a battery, the electrolyte being the tissue fluid; there is corrosion and therefore loosening of the metal. Pure metals are inert, but any metallic appliance made of galvanized iron, plated steel, or metallic alloy containing a metal exposed to active body fluids will cause galvanic action. The electrolytic action leads to the liberation of irritating metallic salt solutions in the body fluids; these in turn cause excessive proliferation of cellular and fibrous tissue but inhibition of bone growth. Venable found that vitallium is an alloy free from electrolytic action, and therefore best suited for screws in bone.

The importance of circulatory changes in modifying the structure of bone is emphasized by the work of Leriche and Policard, whose views on the formation of bone depart widely from those commonly accepted. They consider that calcium is deposited in a firm homogeneous material (preosseous substance) from the surrounding lymph, and that ossification depends not on the activity of osteoblasts, but on an adequate blood supply and an adequate supply of calcium. Hyperemia is followed by decalcification, lessened circulation by osteosclerosis, and loss of blood supply by necrosis. Examples of the application of these principles to the pathology of bone will be found in Greig's excellent monograph on the Surgical Pathology of Bone.

An interesting form of osteoporosis is that produced by long-continued loss of bile through a biliary fistula. This can be produced constantly in the experimental animal, and occasionally occurs in the human subject accompanied by loss of weight, cachexia and finally death. An extreme degree of osteoporosis amounting to osteomalacia can be produced in the dog in this way, the bones chiefly affected being the ribs, radii and vertebrae. In addition to these skeletal changes there is often hypertrophy of the parathyroids—evidently a secondary phenomenon. Many explanations for biliary fistula osteoporosis have been advanced, but none are sufficiently convincing to be considered here.

The Transplantation of Bone.—The fate of a bone which is transplanted from one part of the body to another or from one body to another is of great practical importance. When a bone is transplanted to another position the greater part of it dies. That the bone cells are necrosed is

evidenced by their shrunken appearance in the lacunae, which in many instances appear to be quite empty. But not all the bone cells share this fate; only those which are totally cut off from a supply of nourishment. Those which are still bathed by the lymph and body fluids continue to live, and these are the all-important bone-forming cells on the surface, lining the medullary cavity, and at the mouths of the Haversian canals. These osteoblasts, especially those lining the medullary cavity, show marked proliferation in the course of a few days. The cut ends of the graft show much less activity. Only the cells at the openings of the Haversian canals proliferate, and if there are no such openings there is no new bone formation.

The next step, as Gallie and Robertson have shown, is a vascularization of the necrosed bone. New vessels grow in from the surrounding tissues, make their way along the Haversian canal, and revascularize the bone. At the same time the proliferating osteoblasts accompany the new vessels, giant cells make their appearance, and the dead bone becomes absorbed by these cells and converted into a series of spaces lined by osteoblasts. These cells now commence the formation of new bone. The graft thus becomes absorbed and at the same time replaced.

These changes are entirely dependent on the activity of the osteoblasts. If the graft is first boiled and the osteoblasts killed, the graft will be vascularized, but neither absorption nor new bone formation will occur. If, however, the boiled bone is brought in contact with osteoblasts, it will be invaded in the same way as is the unboiled. Thus when only small gaps in healthy bone are to be bridged, as in the case of the spines of the vertebrae, boiled bone may be used, for the osteogenic tissue can completely invade the graft from the margins of the normal bone. Sepsis will effectually prevent all attempts at reconstruction, for the osteogenic cells of the surface are killed by the bacterial toxins.

The two processes are not evenly balanced. For the first six weeks or two months absorption proceeds more rapidly than new formation. If at the end of that period the bone has some function to perform, the process of absorption will give way to the process of reconstruction. On the other hand if the bone is implanted in muscle, where it has no work to do, the absorption process continues to have the upper hand, until by the end of six months the graft is merely represented by a fibrous-tissue scar.

The activity of the osteogenic process will depend on the amount of surface with which the lymph can come into contact. In the case of cancellous bone such as rib, the reparation process will be much further advanced by a given date than when compact bone is used.

When a heterogeneous graft is used, that is to say one from a different species, not only will the main body of the graft die, but also the osteogenic cells, for they do not find suitable nourishment in the lymph which bathes them. Even when a graft from another individual of the same species is used the properties of the nutritive fluids must be considered. It is known that skin grafts take better if the two persons concerned, the donor and the recipient, belong to the same blood group. The same may be true of bone grafts. If, therefore, the graft has to be taken from another person, it would be well to choose one belonging to the same blood group.

Healing of a Fracture.—This takes place in three stages: (1) granula-
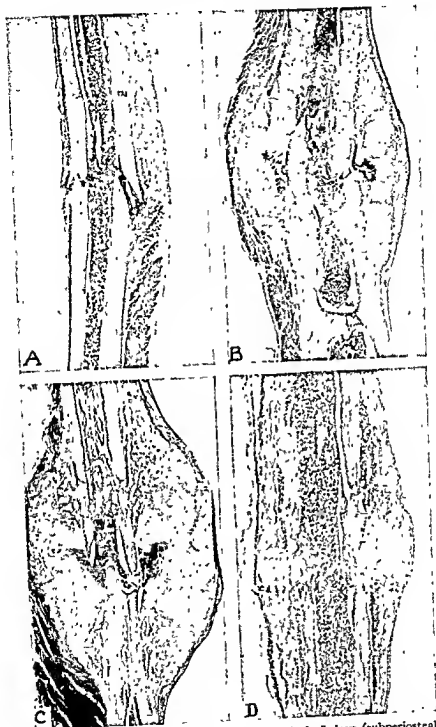
Fig. 439.—Healing of experimental fractures. X 14. A, 3 days (subperiosteal osteo-blasts). B, 7 days (osteoid). C, 15 days (abundant callus). D, 6 weeks (diminished callus being converted into bone).

tion tissue forms in the exudate between the broken ends of bone; (2) this becomes converted into osteoid tissue; (3) calcium salts are deposited in the osteoid tissue with the formation of bone.

As the result of tearing of the periosteum and the surrounding tissues, blood is poured out, a certain amount of inflammation occurs, and a mixture of blood clot and inflammatory exudate is formed around and between the broken ends of bone. The amount of this exudate, which will determine the amount of subsequent callus formation, is dependent largely upon the accuracy of apposition of the two fragments. If little or no space is left and the line of the fragments is good there will be a minimum of exudate. If the gap is large, or the fragments override one another, the exudate will be correspondingly bulky. The exudate is quickly invaded by cells and new capillaries, and a kind of granulation tissue is formed. The new cells are fusiform osteoblasts derived partly from the deeper layer of the periosteum, partly from the cortical layer of bone, as shown originally by Macewen and confirmed later by Gallie and Robertson (Fig. 439A). The proliferation of osteoblasts is of an extraordinarily rapid and massive
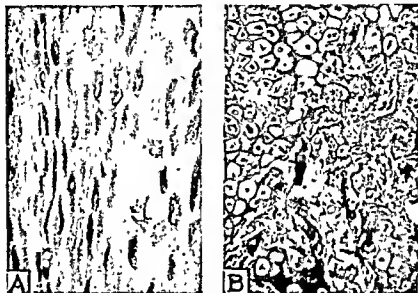
Fig. 440.—A, Proliferating osteoblasts. × 520. B, Cartilage formation. × 130.

character as can be seen in a series of experimental fractures examined at 24 hour intervals; indeed there is no other non-malignant process which is quite comparable with it.

In the course of four or five days this becomes converted into *osteoid tissue*, which is tissue resembling bone in its structural arrangement with a homogeneous matrix but not possessing any lime salts (Fig. 439B). The osteoid tissue is scattered here and there in little clumps, and in the intervening spaces marrow-like tissue develops. The osteoid tissue or callus becomes increased in amount and acts as an efficient splint (Fig. 439C). Finally lime salts are laid down, and the ends are knit together by fully formed bone (Fig. 439D). Low blood calcium produced by deficient diet does not slow the rate of healing or lead to non-union.

In the immediate neighborhood of the fracture the bone cells die. Near the fracture the osteogenic cells proliferate in massive fashion (Fig. 440A).

and may form cartilage instead of bone (Fig. 440B). This cartilage formation is most marked when there is movement or separation of the fragments. The new cartilage is invaded and replaced by bone. This is ossification in cartilage, as compared with the process just described which corresponds to ossification in membrane.

The healing of fractures may be interfered with in a number of ways. Sepsis, which is so often present in a compound fracture, always causes great delay. Fragments of muscle, fascia, or fat may intervene between the two fragments. Wide separation of the fragments renders the process of healing a long one, and the resulting union insecure. In all such cases the bond of union, if it occurs at all, is apt to be fibrous or cartilaginous rather than osseous, and the limb is unable to sustain any strain.

The mass of new tissue formed at the seat of a fracture is known as *callus* on account of its hardness. The callus may be *external*, ensheathing the broken ends as a plumber's solder ensheaths a junction of pipes; *intermediate*, forming a direct union between the fractured surfaces; and *internal*, filling up the marrow cavity. The intermediate callus is the only form which persists. The internal and the external callus are in due time removed.

For the process of healing is by no means finished when the gap is patched and the ends united. A slow process of molding ensues which may last for years. The removal of the internal and external callus is undertaken by large multinucleated cells known as osteoclasts, and this work is done so efficiently that it may be impossible to detect the site of the fracture. But for a long time afterwards a process of internal adjustment goes on whereby the somewhat haphazard preliminary arrangement of the bone lamellae becomes molded so that it conforms to the stresses and strains to which the part is subjected.

INFLAMMATION OF BONE

In inflammation of bone, more perhaps than in any other tissue, the balance struck between the processes of destruction and repair is all important. If the infection is so slight that resolution occurs, no trace will be left of the struggle, although pain and other clinical phenomena may point unmistakably to its occurrence. If the infection is overwhelming death of the part will occur en masse, a process of *necrosis*, favored by the factors already mentioned, and comparable to sloughing or gangrene in soft tissues. The dead portion of bone which gradually becomes separated from the lining is called a *sequestrum*, and imparts a characteristic gritty sensation to an examining probe.

Often, however, the balance is more evenly maintained, and an inflammatory granulation tissue is formed in the medulla, the Haversian canals, and the interstices between the laminae, which exerts an eroding action on the hard bone with a resulting molecular death, rarefaction, or *caries*, so that the bone becomes, as it were, worm-eaten; some parts are taken and others are left. The process, which corresponds to ulceration in soft tissues, may occur in subacute pyogenic infections, but is characteristic rather of the more slowly acting poisons of tuberculosis and syphilis. This same process of rarefaction it is which, acting around the margin of a mass of dead bone, gradually separates it from the living tissue and gives rise

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to a sequestrum. Much of the destructive action is carried on by osteoclasts, large phagocytic cells whose function in health it is to mold the growing bone in conjunction with the formative cells, the osteoblasts of the periosteum. Both necrosis and caries are manifestations, differing in degree, of the second variety of inflammation.

Healing with fibrosis in bone takes the form of sclerosis, a process of new bone formation in the cancellous spaces and in the walls of the Haversian canals, which may be slight in degree or may be so extreme as to dominate the whole picture. The new bone is denser than the old, and in that respect, as well as in the sites in which it occurs, it is abnormal. When a section of the shaft of a long bone dies it becomes surrounded by a layer of dense new bone called the *involucrum* or new case, which may be perforated here and there by tunnels called *cloacae* running down to the sequestrum. When the lesion is more localized the reparative process may take the form of small spicules of bone projecting from the surface.

The balance between the forces of destruction and conservation may be such that a zone of densely sclerosed bone is formed around a small focus of softening in which bacteria may contrive to eke out an existence for many years. Such a circumscribed bone abscess is known as a *Brodie's abscess*.

It will thus be seen that there are four possible courses which pyogenic infection of bone may follow: (1) resolution; (2) a fulminating course; (3) the course of an ordinary osteomyelitis; (4) the formation of a Brodie's abscess.

The processes of destruction and sclerosis go hand in hand, but naturally the relative proportions vary greatly in different cases. In tuberculosis, in which caries is always well marked, sclerosis is seldom a prominent feature. In syphilis, on the other hand, the slowly acting spirochetes usually call forth an excessive amount of new formation.

The method of *spread* also varies in different infections. The suppuration of pyogenic infection readily passes through the open structure of the cancellous metaphysis, down the medullary cavity, along the surface under the periosteum, and from the surface to the marrow via the Haversian canals, so that it is doubtful if a pure infection of either the periosteum or the medulla can ever occur. The epiphyseal cartilage appears to present a formidable barrier to the spread of the infection, so that, even though the disease frequently commences in the metaphysis, infection of the joint is a comparatively rare occurrence. Tuberculosis behaves in just the opposite manner. The process, again usually commencing in the metaphysis, remains fairly well localized with little tendency to spread down the medullary cavity, but invasion of the joint is the rule rather than the exception.

OSTEOMYELITIS

Acute pyogenic inflammation involves all the constituents of a bone, although it may be in different degree. It is a mistake to consider periostitis and osteomyelitis as separate diseases. There are two main types, hematogenous and exogenous. The hematogenous type is that commonly seen in civilian life; it is this form which is discussed in the following paragraphs. The exogenous type is seen in compound fractures and is particularly common in war injuries; it is not so rapid, virulent or destructive

as the hematogenous type. The exogenous type is single, the hematogenous type may affect a number of bones.

Etiology.—The *predisposing* causes are age, sex, and trauma. The great majority of acute infections occur during the period of active growth, being commonest between the ages of two and ten. The disease is three times as common in boys as in girls, probably because the former are more exposed to trauma. A history of some form of trauma, a blow or a strain, is often obtained. When a wrench is applied to a growing bone the part most likely to give way is the metaphysis, in which an effusion of blood may occur offering a suitable nidus to any waiting bacteria. It cannot be denied that trauma may act as a true etiological agent, but it is safe to say that in the vast majority of cases any recent trauma in the neighborhood is purely coincidental.

The *exciting* cause is one of the pyogenic organisms, usually Staphylococcus aureus, less frequently Staphylococcus albus, and occasionally streptococcus, pneumococcus, and typhoid bacillus, the last deserving a separate paragraph to itself. The infecting organism is carried to the bone by the blood stream. It enters the circulation from one of the usual septic foci in the body, of which the mouth and tonsils are probably the most important. Occasionally suppuration of the skin, boils, infected wounds, or compound fractures may act as the source of infection. Suppuration may spread to the mastoid process from the middle ear.

John Fraser has drawn attention to the importance of the pneumococcus as a cause of osteomyelitis. In a series of 400 cases, 14 per cent were due to this organism. It affects babies and young children, the evidences of toxemia and the leucocytosis are comparatively slight, the associated joint is usually the site of a serous effusion, and the bone inflammation is of a serous or albuminous rather than a suppurative type. It is evident that treatment does not require to be so drastic as in the acute suppurative variety.

The long bones are most frequently affected, particularly the upper and the lower end of the tibia, the lower end of the femur, and the upper end of the humerus. Almost any bone may occasionally be involved, even the vertebrae.

The point at which inflammation commences depends on the age of the patient. It is convenient for many purposes to distinguish two types of the disease, the juvenile and the adult. In the former the bone is still growing, and the epiphyses are still present. In the latter the development of the skeleton is complete. In the juvenile group the process almost invariably commences in the metaphysis. The reasons for this predilection are two-fold: (1) this region possesses a peculiarly rich blood supply, and the vessels present the hair-pin bends already described; (2) it is this region which suffers most in twisting injuries to the joint. In the adult group the lesion may commence in any part of the bone. The liability of the metaphysis to infection in the young is strikingly exemplified in a case recorded by Gibson. A boy, aged 12, developed evidence of acute inflammation in the left clavicular area, but nothing was found at operation. The autopsy revealed a small abscess at the root of the coracoid process of the scapula. The coracoid process has an epiphysis which remains separate until the fifteenth year.

The juvenile differs from the adult form in other respects. The juvenile cases are sometimes fulminating, ending fatally within 24 hours. The adult cases are never so acute. The juvenile cases always commence as an osteomyelitis; any periostitis is secondary. In the adult cases a primary periostitis may occur.

Spread.—It used to be believed that infection spread rapidly down the medullary cavity till the greater part or the whole of the shaft was involved. From a study of experimental and clinical material Starr showed medullary cavity till the greater part or the whole of the shaft was involved.
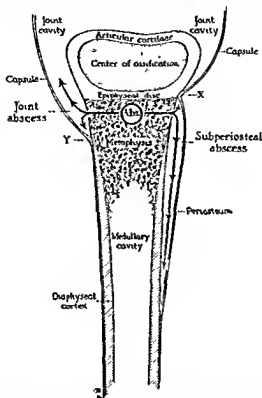
Fig. 441.—Diagram illustrating the usual course of spread of infection in acute hematogenous osteomyelitis. X represents the point of firm attachment of capsule and periosteum in the region of the epiphyseal disc when the metaphysis is extracapsular. Y is the fixation point of capsule and periosteum when the metaphysis is intracapsular. (Hart. J. A. M. A., Feb. 13, 1937.)

From a study of experimental and clinical material Starr showed that infection commences in the metaphysis and extends along the epiphyseal line to the cortex and periosteum. (Fig. 441.)

The pus formed under the periosteum strips it from the bone at an early stage, and proceeds to make its way along the shaft between the periosteum and the bone. As the result of the increased tension the pus probably spreads backward through the Haversian canals at different levels and invades the medulla from the cortex, giving a "spotty" character to the shaft infection. Thus instead of the periosteum covering the shaft being

infected from the medulla, it is the medulla which is infected from the periosteum. Direct spread into the medulla from the original focus in the metaphysis is not an early occurrence, owing partly to the distance which separates the two in the case of a long bone. This intervening tissue was found free from bacteria in the human cases which were examined bacteriologically. The firm attachment of the periosteum to the epiphyseal line in the child prevents the spread of the pus into the joint.

Fig. 442.—Acute infectious osteomyelitis. Marrow of the shaft of the tibia almost entirely infiltrated with purulent exudate. The thickening of the cortex of the shaft is due to a deposit of periosteal bone. The upper epiphyseal line has been perforated, and the epiphysis is infiltrated with purulent exudate. (E. H. Nichols in Keen's Surgery.)

Fig. 443.—A, Rough and pitted sequestrum, B, Smooth sequestrum covered by new bone five years after acute osteomyelitis (Greig, Surgical Pathology of Bone).

Morbid Anatomy.—The process is a suppurative one, the medulla becomes converted into an oily pus owing to destruction of the fatty tissue (Fig. 442), and the surface of the bone is bathed in pus which also fills the Haversian canals. At first the surface, from which the periosteum is raised, presents the usual healthy shining appearance, but soon it becomes of a dull opaque white, and at a later date, when a *sequestrum* has formed, it may be of a dark brown color; the surface is usually rough and pitted owing to the erosive action of the granulations lining the deep surface of the new case. As long as the surface is separated from the periosteum by a layer of pus it remains smooth (Fig. 443). Thrombosis of the veins is

constant, and in addition to still further interfering with the supply of nourishment to the part, the septic thrombi thus formed may occasionally give rise to emboli and general pyemia, of which ulcerative endocarditis may be a feature and may still further increase the gravity of the condition. Blood culture is positive, and sometimes the septicemia is so overwhelming that death may occur within two or three days of the onset of local symptoms.

Fig. 444.—Abscess of lower end of tibia rupturing into ankle joint. A black rod passes through the perforation which was much smaller in the fresh specimen.
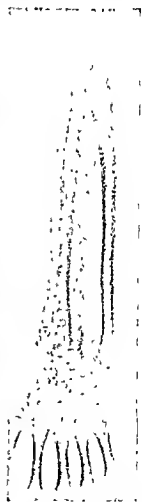
Fig. 445.—Acute osteomyelitis. Extensive involucrum surrounds radius.

The adjacent joint may become filled with a sterile serous effusion, or the process may rupture into the joint and cause a purulent arthritis. (Fig. 444.)

The dead sequestrum becomes separated from the living bone, and lies either in a pool of pus or in a cavity enclosed by a *new case* or *involucrum* which is laid down by the periosteum and which takes the place of the dead bone (Fig. 445). The involucrum is perforated here and there by *cloacae*, through which pus continues to discharge. Sinuses extend from the cloacae to the skin, and through these sinuses pus may escape

Fig. 446.—Osteophytic roughening of bone in osteomyelitis.

Fig. 447.—Marked new bone formation following osteomyelitis

for many years, for as long, indeed, as the sequestrum remains in position. Fragments of necrotic bone may be discharged through the sinuses. The long-continued inflammation stimulates the periosteum to continued activity which may result in the formation of osteophytes with great roughening of the bone (Fig. 446), or in a general thickening and condensation of the shaft, which may become very thick and heavy (Fig. 447), a feature which is even more striking in syphilis.

Unfortunately the patient with osteomyelitis is by no means out of the woods when one lesion has been disposed of, because the staphylococci may settle in some distant bone, causing a fresh focus of infection. This process may go on, involving one bone after another, sometimes ending in a general septicemia. Or the infection may light up again in the original lesion. In one of my cases there was an interval of 38 years between the original attack at the age of nine and the final fatal attack.

There is a rare variety of sequestrum formation in which the medullary cavity is lined by a thin tube of dead, densely hard bone, which may be readily separated from the living bone of the shaft. In such a case it would almost seem as if there had been a primary infection of the medulla of the bone.

Bones developed in membrane, as the flat bones of the skull and the upper jaw, are not reproduced to any extent. Where the periosteum has been completely destroyed no new bone is formed, so that the new case may be of a patchy character. Occasionally the cavity left in the bone shows the phenomenon known as epithelization, i. e., it becomes lined by squamous epithelium from which in rare cases an epidermoid carcinoma may arise. The epithelial cells come from the skin, having grown along and lined first the sinus and then the cavity in the bone.

Chronic Osteomyelitis.—When a bone has once been infected, the bacteria may lurk in its depths for months or years, giving rise to recurring attacks. This relapsing form of osteomyelitis is especially common in adults.

A chronic circumscribed abscess, called a *Brodie's abscess*, may form in one of the ends of a long bone, it may be years after the original infection. The common site is the upper end of the tibia, but the lower end of the femur, the upper end of the humerus, and other parts, may also be affected. During periods of quiescence there is a small cavity containing clear, serous, sterile fluid, and surrounded by a zone of densely sclerosed bone, casting a deep shadow in the X-ray picture, but when the process becomes active the cavity becomes filled with greenish-yellow pus from which the staphylococcus can be isolated, and it is lined by a layer of granulation tissue.

Typhoid Osteomyelitis.—Mention has already been made of the typhoid bacillus as a cause of osteomyelitis. The bone marrow may readily be infected in such a septicemic condition as typhoid fever, but the bacilli rarely succeed in establishing themselves. When symptoms appear it is usually about the end of the second month, but there is no form of bone disease in which the infection may be more latent, and it may be many years before signs of inflammation manifest themselves. The bacilli have been obtained in pure culture as many as 20 years after the original infection. The bones usually involved are the upper end of the tibia, the ribs and the sternum.

The pathological lesion is somewhat variable, but usually consists of a collection of greenish or brownish pus under the periosteum, in the metaphysis, or in the shaft. The condition may be subacute or chronic. Sequestrum formation is rare, for the process is rather one of molecular death than death en masse, of caries rather than necrosis.

Coccidioidal Osteomyelitis.—A form of acute osteomyelitis often mistaken for pyogenic and tuberculous lesions of bone is caused by Coccidioides immitis, a fungus found mostly in California, especially amongst those who have visited the San Joaquin Valley. The fungus enters the body through the skin and respiratory tract, and is carried by the blood to the bones and other organs There is necrosis and abscess formation without any new formation of bone. The mortality is about 50 per cent due to involvement of the lungs

*Sclerosing Non-suppurative Osteomyelitis of Garré—*This rare form of acute osteomyelitis was first described by Garré in 1891. The onset of the disease is usually acute, with high fever, swelling of the limb, pain at the site of the bone lesion, and infiltration of the soft parts. There is, however, no formation of pus, nor is the overlying skin reddened. When the acute symptoms subside the bone is left permanently thickened. The affected bone is very dense, and the medullary cavity is obliterated, giving a striking radiographic picture, which however, is apt to be confused with that of syphilis of bone. The etiology of the disease is not known.

TUBERCULOSIS OF BONE

Bone tuberculosis is a chronic inflammatory condition, an osteomyelitis with secondary periosteal involvement, occurring in early life, choosing particularly the ends of the long bones, the short long bones, and the short bones, displaying as a rule an excess of bone destruction over bone formation, and yet with a decided tendency towards limitation of spread and spontaneous healing owing to the fibrous tissue formation so characteristic of tuberculous disease in the lungs and other organs.

Site of Infection.—The infection is carried to the bone by the blood stream, probably in the form of a tuberculous embolus, from some other focus in the body. Tuberculosis commences in cancellous bone, seldom in compact bone, and the most frequent victims are the ends of the long bones, especially the tibia and femur (Fig. 448), the short long bones, the short bones of the carpus and tarsus, and the vertebræ. As all of these are in close proximity to joints, bone and joint tuberculosis are very frequently associated.

The first part to be affected is usually the metaphysis or epiphysis of a long bone. Both of these are richly supplied with capillary loops in which an infected embolus may readily lodge. The circulus vasculosus, containing the vessels responsible for carrying the infection, lies in the reflexion of the synovial membrane on to the bone. When the reflexion includes the metaphysis, as at the upper end of the femur, the disease will originate in that part. When, on the other

Fig. 448.—Tuberculosis of head of femur; the articular cartilage has been stripped off.

hand, the reflexion lies entirely in relation to the epiphysis, as at the upper end of the humerus, and, to a lesser extent, at the lower end of the femur, the primary focus will be in the epiphysis.

There is a further factor which may well determine which bone is to be attacked. In tuberculosis, say of the lungs, there is frequently an obliterating endarteritis of the vessels in the marrow due to the circulating tuberculous toxins, which diminishes the blood supply, gives rise to a cell sickness, and so predisposes the part to invasion by the tubercle bacillus. This endarteritis is irregular in its distribution, thus resembling arteriosclerosis, and one bone may be taken while another is left.

The Primary Bone Lesion.—The bacilli reach the marrow of the cancellous bone in a metaphysis or epiphysis by one of two routes: (1) an

intravascular route, in which the bacilli are carried by the blood stream into the center of the bone; (2) a perivascular route, in which the infection commences in the synovial membrane of the joint, and spreads slowly along the perivascular lymphatics to the interior of the bone.

A miliary tubercle is formed composed of a central mass of endothelial cells and a surrounding zone of lymphocytes. It appears as a small grey point. As fresh tubercles are formed and the disease spreads, characteristic changes occur in all the constituents of the bone, and these may now be briefly considered.

The *marrow* around the focus shows the tissue changes one is accustomed to associate with tuberculosis in the lungs and elsewhere. For the first week the response is that to an acute irritant, and a leucoblastic

Fig. 449.—Tuberculosis of lower end of tibia.

reaction on the part of the marrow gives rise to great numbers of polymorphonuclears. The tuberculous toxins then begin to make their presence felt, and the lymphocyte replaces the polymorph. Later still the fibrosis which plays so important a part in the limitation of tuberculosis begins to develop, the fat is replaced by connective tissue, and in time the original focus becomes walled off by a dense zone of fibrous tissue, which is yellowish-white in color and remarkably firm to the touch. Invasion of the focus by the fibrous tissue may eventually bring about complete cure.

The *bone lamellae* show two characteristic changes, osteoporosis or rarefaction and osteosclerosis or condensation (Fig. 449). These merely correspond to tissue destruction and fibrosis in tuberculosis elsewhere. *Osteoporosis* or caries is brought about by two agencies: (1) the action

of osteoclasts, and (2) the erosive influence of a cellular granulation tissue which is formed in relation to the blood vessels, and which enlarges the Haversian canals and erodes the bone under the periosteum and in contact with the medulla (Fig. 450). Branching trabeculae of bone are left, the interspaces being filled with granulation tissue. *Osteosclerosis*, which is seldom marked in tuberculosis, being much more characteristic of syphilis, is the analogous process in the bone to fibrosis in the marrow. Through the action of osteoblasts fresh layers of bone are deposited on the surface of the laminae, so as to increase their thickness and consequently the denseness of the bone.

The *periosteum* is early stimulated to activity, owing to the increased vascularity, the result of the underlying bone disease. The character of the new bone formed is peculiar; it is usually quite cancellous, and only

Fig. 450.—Tuberculosis of bone with marked destruction. × 120.

compact close to a joint where movement would be interfered with by the more abundant porous bone. If new bone were deposited directly on the smooth surface of the shaft it would be but poorly attached and would readily be broken off. The osteoclasts, therefore, which are found on the deep surface of the periosteum, first excavate a series of holes along the shaft, until the smooth surface has become quite rough. The osteoblasts now deposit bone upon the roughened surface. This new bone is not laid down uniformly but in the form of arches, between which there is a small quantity of granulation tissue. A series of tiers of arches is thus formed, an architectural device by means of which a maximum of strength with a minimum of weight is obtained.

Progress of the Disease.—Tuberculosis may behave in various ways in bone as in other organs. It is unnecessary, however, to introduce a

special series of names to denote the different varieties. It will be sufficient if we recognize a localized form and a spreading form, with a third variety which deserves special consideration, the atrophic form or caries sicca.

The *localized form* is much the commoner. The defense is sufficiently strong to hold the disease in check. It corresponds to a localized nodule in the lung. The lesion, usually about the size of a marble, presents a center which is either caseous or converted into a semi-fluid material. Around there is a pale pink zone, blending with the surrounding marrow. This is the limiting band of new fibrous tissue. The condition is essentially chronic, so that the slow process of rarefaction or caries, due to the activity of osteoclasts and granulation tissue, usually results in complete absorption of the lamellae. If, however, separation of the lamellae occurs before absorption is complete, they become necrosed and form small sequestra.

The *spreading form* may be described as a tuberculous osteomyelitis in which the fibrosis is insufficient to limit the spread of the disease. It corresponds to a diffuse tuberculosis of the lung. The central caseous mass is surrounded by a zone of grey infiltration, representing tuberculous granulation tissue which has not yet become caseous. Around this again there is a red zone of reaction. Thrombosis of the vessels occurs at an early stage and greatly weakens the resisting power. Rarefaction is not a marked feature, for before it has time to proceed far necrosis supervenes, active processes are arrested, and comparatively large sequestra are formed. The periosteum, as usual, displays marked activity, and lays down an abundant supply of new bone.

The disease may spread down the medullary cavity, until the greater part or the whole of the shaft is involved. It may spread through the epiphyseal cartilage, involving the epiphysis and the adjacent joint. It may spread to the periosteum, where it forms a subperiosteal cold abscess, and may then involve the soft parts, giving rise to a cold abscess which may ultimately discharge on the skin.

Where the medullary spread is a marked feature the shaft of the bone may become much swollen and expanded, owing to absorption of the interior of the bone by granulation tissue and deposition of new bone on the surface by the periosteum. This is best seen in *tuberculous dactylitis*, in which a metacarpal bone or more commonly a phalanx presents a spindle-shaped swelling known as spina ventosa, which must be differentiated from the similar swelling produced by congenital syphilis.

Caries Sicca.—This is a rare condition, chiefly affecting the upper end of the humerus. The deeper portion of the bone becomes rarefied owing to the formation of granulation tissue, and new bone is deposited on the surface, which itself, however, becomes in turn eroded. Finally the granulation tissue becomes dried up and fibrosed. True suppuration never occurs.

Tuberculosis of the Vertebrae (Pott's Disease).—The vertebrae are affected by tuberculosis more frequently than any other bones in the body. The disease was first described by Percival Pott in 1779, and since that time it has been known by his name. The disease is commonest in children, particularly during the first 5 years of life. The site of election is the lower dorsal and upper lumbar regions, especially the last three dorsal

and the first and second lumbar vertebrae. The disease may be limited to one vertebra, but as a rule two and sometimes several adjoining vertebrae are involved (Fig. 452). The intervertebral discs are destroyed as well as the bodies of the vertebrae, in this respect differing from malignant disease of the spine, a point of value in X-ray diagnosis (Fig. 453). It is very exceptional to find two separate foci in different parts of the spine.

The interior of the body of a vertebra is supplied with blood by a branch from the posterior spinal artery which enters the posterior surface of the bone. For this reason, particularly in children, the initial lesion is usually in the center of the vertebral body. A limited area of the front of the body is supplied by branches from the intercostal or lumbar arteries, and as in
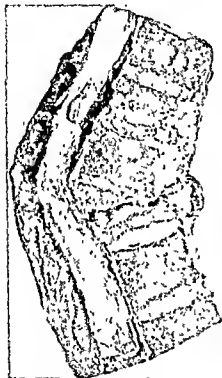
Fig. 451.—Tuberculosis of spine; deformity and destruction of bodies and discs.

Fig. 452.—Tuberculosis of bodies of vertebrae.

the adult this supply is more abundant, the adult lesion is often peripheral in type. Two main forms of the disease may therefore be recognized, the central and the peripheral. The *central form*, which is very much the commoner and is the only form seen in children, begins in the center of the body, which gradually becomes hollowed out (Fig. 454) until it is no longer able to support the weight of the vertebrae above and collapses, giving rise to an angular deformity (Fig. 451). One or more vertebrae may be involved. The *peripheral form* affects that portion of the anterior surface which is supplied from the intercostal or lumbar vessels (Fig. 455). It is only found in adults, and as it leaves the greater part of the body of the vertebra intact, it causes little or no deformity. In rare cases the initial lesion is in the spine, laminae or transverse processes.

The peculiar susceptibility of the spine to tuberculosis has not been explained. Pyogenic bacteria rarely cause disease of the spine and frequently attack the long bones, whilst about one-half of all skeletal tuberculosis occurs in the spine. There are other facts which throw doubt on the hematogenous origin of spinal tuberculosis. It is possible that adjacent lymphatic tissue may be a source of some importance.

Results.—These are three in number: (1) the production of a spinal deformity, (2) dissemination of the tuberculous pus, and (3) involvement of the spinal cord.

The *deformity* is a kyphosis, but some scoliosis may also be present. The collapse of the bodies of the vertebrae causes a backward angulation, the degree of which varies in different parts of the spine. In the cervical

Fig. 433.—Tuberculosis of vertebrae showing destruction of bone and narrowing of intervertebral space.
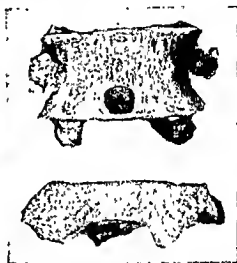
Fig. 454.—Central form of tuberculosis of spine. The upper vertebra shows a cavity, the body of the lower vertebra is partially destroyed

and lumbar regions it is seldom pronounced, but in the dorsal region it may be very marked. When the angulation is acute the spinal canal may be considerably narrowed.

The *dissemination of pus* depends on anatomical arrangements. The tuberculous process breaks through the bone and gives rise to the formation of a *cold abscess*. Under appropriate treatment this may undergo absorption. Or it may spread to a considerable distance. In the *upper cervical* region the pus passes forward and appears in the posterior wall of the pharynx as a retropharyngeal abscess. Being behind the prevertebral fascia it seldom bursts into the pharynx, but passes laterally into the posterior triangle of the neck. In the *lower cervical* region the abscess *may* press the esophagus and trachea forward; it passes laterally into the posterior triangle. It may pass downward and enter the posterior medias-

tinum. In the lower *dorsal* region, the usual site of Pott's disease, the pus commonly enters the sheath of the psoas muscle to form a psoas abscess. It may follow the anterior primary division of the spinal nerves along the intercostal space, and come to the surface at the side of the chest or even the front, so that the condition is apt to be mistaken for tuberculosis of the rib unless the back is examined. In rare cases the pus may pass back between the ribs with the posterior divisions of the nerves. In the *lumbar* region the pus usually forms a psoas abscess, but may pass backward and point under the skin.

A *psoas abscess* is caused by the pus from a lesion in the lower dorsal or upper lumbar vertebrae entering the sheath of the psoas, *which is attached internally to the bodies of the vertebrae*. In the psoas muscle the abscess increases in size, and there may be two or three pints of thick caseous material. This may extend in different ways and appear on the surface in a variety of places. It may come to the surface in the lumbar region, may extend into the iliac fossa, may pass behind Poupart's ligament and point in the groin where it is apt to be mistaken for a femoral hernia, and in rare cases it may extend down the inner side of the thigh and appear in the popliteal space.

If the primary focus in the bone is in front of the attachment of the psoas sheath to the vertebrae, the pus will not enter the psoas, but will pass into the iliac fossa to form an *iliac abscess*, which points in the neighborhood of the anterior superior iliac spine. Rarely the pus may pass into the pelvis and form an *ischio-rectal abscess* or even a *gluteal abscess* in the buttock.

Involvement of the spinal cord is not common. The usual cause of compression of the cord is inflammatory edema and tuberculous infiltration of the meninges. This may cause paralysis of the legs owing to pressure on the cord, but when the weight is taken off the spine by the horizontal posture, complete recovery is the rule. A cold abscess may form under the posterior common ligament, and, gradually passing backward, come to press on the cord. The angular deformity of the spine is not sufficient of

Fig. 455.—Tuberculosis of spine; extensive periosteal involvement; no deformity.

itself to cause pressure paralysis, for sufficient room is left to accommodate the cord.

The paralysis which may complicate the later stages of the disease is not due to the angular deformity of the spine, but to an edema of the meninges, or to the cold abscess which forms under the posterior common ligament, and, gradually passing backward, comes to press upon the spinal cord.

The pus may trek in almost any direction. It may pass along a rib under the periosteum and appear at a considerable distance from the original focus, so that in every case of tuberculosis of a rib the spine should be carefully examined. Or it may pass down within the sheath of the psoas muscle and appear as a psoas abscess under Poupart's ligament.

In the skull the disease usually commences in the diploe, and extends outward so as to perforate the outer table.

Harris and Coulthard have analyzed the complications arising in the course of Pott's disease as regards frequency with the following results. In 80 cases abscess developed in 90 per cent, amyloid disease in 14 per cent, renal or genital tuberculosis in 26 per cent, active pulmonary tuberculosis in 30 per cent, paraplegia in 18 per cent, and Addison's disease in 4 per cent.

SYPHILIS OF BONE

Syphilis of bone differs from tuberculosis in that it affects different parts—the diaphysis of long bones rather than the articular ends—involvement of joints very seldom occurs, and sclerosis is much more prominent than rarefaction, whereas in tuberculosis the reverse is the case. Patients with syphilis of the bones seldom develop neurological manifestations, a fact which supports the view that there are different strains of spirochetes, some with an affinity for ectodermal, others for mesodermal structures.

The bones may be affected either in acquired or in congenital syphilis. The acquired form will first be described, and the lesions peculiar to the congenital variety considered later. The fundamental pathology of both forms is identical.

The bones most commonly involved are the tibia, the sternum, the skull, and the bones of the face. Recent work has shown that the vertebral column, especially the cervical portion, is much more frequently involved than used to be supposed. Although it is improbable that the spirochetes are entirely limited to one part of the bone, the brunt of the attack may fall on the periosteum or on the marrow in the medulla, so that we may speak of a periosteal and an endosteal form of the disease. The periosteal variety, at least in its clinical manifestations, is much the more common.

Periosteal Form.—The spirochetes settle particularly in the vascular tissue of the deeper layers of the periosteum. The tibia may be taken as a typical example (Fig. 456). The usual perivascular infiltration of round cells occurs, and soon an abundant highly cellular granulation tissue is formed around the vessels, not merely in the periosteum but also in the Haversian canals. A transient periostitis associated with nocturnal boring pains is common in the early secondary stage of the disease, affecting particularly the tibia and the frontal bone.

Later in the disease the process is more persistent. The new granulation

tissue erodes the surface of the bone and widens the Haversian canals, giving the bone a highly characteristic worm-eaten appearance, best seen in the case of the skull (Fig. 457). The presence of the spirochetes, however, stimulates the osteoblasts to great activity, and an abundant formation of new bone is laid down: (1) on the surface, where the process may be uniform or where osteophytes suggestive but not pathognomonic of

syphilis may be formed, and (2) on the walls of the dilated Haversian canals, so that the shaft of the bone may become extremely dense and heavy, with obliteration of the medullary cavity.

The thickening may be localized so as to form a fusiform node, or may be diffuse and involve the greater part of the shaft (Fig.

Fig. 456.—Syphilitic periostitis and osteophyte formation. (MacCallum.)
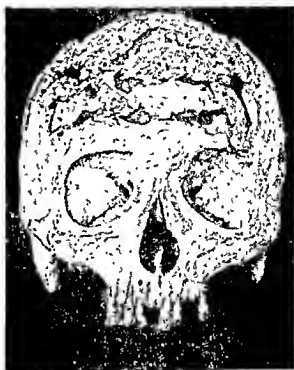
Fig. 457.—Extensive syphilitic necrosis of the calvarium. (Specimen in the Warren Museum of the Harvard Medical School.)

458). This periosteal reaction is usually absent in the skull and other bones which develop in membrane.

Still later interference with the blood supply due to an obliterating endarteritis may lead to degenerative changes in the center of the mass, and a typical gumma is formed. The central part undergoes caseation and softening, and the skin may become involved with the formation of a typical syphilitic ulcer.

The blood supply may be cut off so rapidly that a portion of the bone dies and a sequestrum is formed, which separates but slowly and incompletely from the surrounding bone owing to the comparative inactivity of the rarefaction process. Such a sequestrum is usually very dense and heavy. Considerable areas in the skull, nasal bones, nasal septum, and hard palate may be destroyed in this way, although these late results are seldom seen with modern methods of treatment.

Endosteal Form.—Gummata, gelatinous in appearance and often of a bright yellow color owing to the high fat content, may be formed in the bone marrow. These when small may give rise to no external manifestations. Sometimes, however, and this is particularly the case in the phalanges in congenital syphilis, there may be a diffuse infiltration of the entire marrow with erosion and expansion of the interior of the bone and a corresponding formation of new periosteal bone on the surface. The result is a spindle-shaped swelling, a syphilitic dactylitis, closely resembling in outward appearance the similar condition found in tuberculosis. The shaft of a long bone may be so weakened by this endosteal expansion that a pathological fracture may result. In the rare cases where the articular end of the bone is affected the joint may become involved, with the production of syphilitic arthritis.

The *vertebrae* may be the seat of a syphilitic periostitis or of gummatous formation in the center of the body. Rarefaction rather than caseation is the rule, so that the kyphosis so frequently seen in Pott's disease is less commonly observed in syphilitic disease. As a rule only one vertebra is involved, another point which may serve to differentiate it from tuberculosis. In any case of apparent Pott's disease in an adult it is well to do a Wassermann test.

Fig. 458.—Syphilitic condensation and thickening of the tibia.

Congenital Syphilis.—The bones are more commonly involved in congenital than in acquired syphilis. The lesions of infancy differ from those which develop later in childhood and will be considered separately.

In infancy the important lesions are: (1) epiphysitis, (2) bossing of the skull, and (3) craniotabes.

Syphilitic epiphysitis is a very constant and characteristic lesion in the new-born, particularly affecting the bones about the knee. The normal, thin, pearly-grey line of the epiphyseal cartilage becomes broad, irregular, opaque, yellowish-white, and may be granular and gritty in appearance (Fig. 459). The place of the epiphyseal cartilage is taken by

syphilitic granulation tissue which invades the neighboring young bone, so that when necrosis and caseation occur a mass of minute bony particles results, giving an appearance not unlike that of mortar.

The epiphyseal line instead of forming a union between the epiphysis and diaphysis now becomes a space separating the two, so that growth in length ceases and the infant is unable to use the limb, which therefore appears paralyzed. Indeed the name syphilitic pseudoparalysis has been applied to the condition. Under appropriate treatment, however, firm union will take place and growth in length will again commence.

Bossing of the skull is due to a subperiosteal formation of new spongy bone giving rise to bosses known as Parrot's nodes. These are usually arranged around the anterior fontanelle, giving the so-called "hot-cross bun" appearance. Early treatment results in the disappearance of the bosses, but if the bone becomes sclerosed the condition is permanent.

Fig. 459.—*Syphilitic epiphysitis.* Note the characteristic yellow line. Gross specimen furnished by Professor F. Robert Zeit (DeLee).

Craniotabes is a condition of softening and rarefaction, in which the bone appears to revert to its original membranous state, and may become as thin as parchment. It affects the posterior part of the skull, the occipital and parietal bones. The condition responds well to treatment.

In older children the lesions resemble rather those of the acquired form, and are gummatous in nature.

The *tibia* may be markedly thickened, or it may be compressed laterally and curved forwards, giving the "sabre-blade" deformity.

The *phalanges* may show the combination of endosteal and periosteal involvement already described as syphilitic dactylitis.

The nose and the *palate* are frequently the seat of gummatous formation with resulting destruction, sometimes of a very extensive nature, so that the bridge of the nose may fall in (saddle-nose), and a large perforation of the palate may appear.

TUMORS OF BONE

In the introduction to their fine monograph, on "Tumors of Bone," Geschickter and Copeland point out that it is not sufficient to consider

the constituents of adult bone; the development of bone must also be taken into account. The development of the skeleton is never really complete, for transition forms between the different tissues persist in certain places at all ages, and may serve as the starting point for tumors. Most primary bone tumors, they consider, arise in connection with such transitions in growth. In the lowest vertebrates the skeleton consists of connective tissue, higher in the scale cartilage takes the place of connective tissue, and finally the cartilage gives way to bone. This processional process is repeated in the human embryo, whose skeleton first consists of connective tissue, later of cartilage, and finally of bone. In the case of bones which are developed in membrane, *e. g.*, most of the bones of the skull, there is direct ossification in the primitive connective tissue, the connective-tissue cells becoming changed into osteoblasts which lay down bone. Such bones are not liable to the development of primary tumors. In the case of bones developed in cartilage the process is much more complex. The primitive connective tissue is first changed into fetal cartilage composed of small round cells; this develops into adult cartilage which becomes calcified; the calcified cartilage is removed by giant-cell osteoclasts, canalized and vascularized; finally permanent cancellous bone is laid down. This process goes on actively on both sides of the epiphyseal line, up to adult life on the shaft side, much later in life in the epiphyses. The embryonic connective tissue which has the ability to form both cartilage and bone persists in various places, and is especially abundant in the neighborhood of joints. If these facts be borne in mind, and if it be realized that developmental processes continue well into adult life, the skeletal and age distribution of tumors and the possible types which may occur will be better understood. Geschickter and Copeland use a histiogenetic basis for their classification of bone tumors, somewhat in the same way as do Bailey and Cushing in their classification of the gliomas. "It is in delayed developmental steps in the persisting primitive connective tissue of the skeleton and in conjunction with subsequent histiogenic steps, after the cartilage of the skeleton has been formed, that practically all primary bone tumors take origin."

In studying the difficult subject of bone tumors it is desirable to determine the constituents of the bone from which the various tumors arise. In many cases this is possible; in some it is difficult or impossible. Bone is a connective tissue which happens to be impregnated with lime salts. Anatomically it consists of periosteum, bone, and bone marrow, while at each end of the growing bone there is epiphyseal cartilage. The periosteum consists of *fibrous tissue* and *osteoblasts*. The bone contains *adult bone cells*, which are end-products incapable of proliferating and giving rise to a tumor, *osteoblasts*, and *osteoclasts*. The marrow consists of *marrow cells*, which need not be particularized further, and reticular or *reticulo-endothelial cells*. In general terms, which will be subject to subsequent analysis, it may be said that the periosteal fibroblasts may give rise to fibrosarcoma, the osteoblasts to osteoma or osteogenic sarcoma, the osteoclasts to giant-cell tumor, the cartilage cells to chondroma and chondrosarcoma, the marrow cells to multiple myeloma, and the reticular or reticulo-endothelial cells possibly to Ewing's tumor.

The most satisfactory classification of bone tumors at present available is that suggested by the Registry of Bone Tumors of the American College of Surgeons. The tumors, whether benign or malignant, are divided into two great groups: (1) *osteogenic tumors*, derived from any of the elements concerned in the formation of bone; (2) *non-osteogenic tumors*, derived from tissue residing in bone but not concerned with its formation, such as marrow cells, endothelium of blood and lymph vessels, connective tissue, fat, etc. The osteogenic tumors may be benign, *e. g.*, osteoma, osteochondroma, chondroma, and osteoclastoma (giant-cell tumor), or malignant, *e. g.*, osteogenic sarcoma (osteoblastic and osteolytic), fibrosarcoma, and chondrosarcoma. The non-osteogenic tumors are Ewing's tumor (Ewing's myeloma), myeloma, and periosteal fibrosarcoma.

Osteoma.—It is singularly difficult to know what exactly should be included in the group of osteomata. The difficulty is to determine whether a new formation of bone should or should not be regarded as a true neoplasm. So many inflammatory and traumatic conditions may be associated with bony formation. The callus following a fracture, the new formation in osteomyelitis and syphilis, the ossification of inflammatory exudates in various parts of the body, the condition known as myositis ossificans, the bony outgrowths around joints the seat of chronic arthritis, do not present any essential differences from the masses of bone which are recognized as true osteomas. The histological picture is of little value as a means of differentiation. The gross appearance and the clinical features are the factors most worthy of consideration.

Osteomata usually arise from the surface of the bone; they are then called exostoses. When they arise in the center of the bone they are known as enostoses; these usually occur in the diploe of the skull and the bones of the face.

An osteoma arising from compact bone forms a *compact osteoma*, one arising from cancellous bone forms a *cancellous osteoma*. The former are derived directly from the periosteum and are most frequently found on the skull. The latter are derived from cartilage, and occur chiefly at the articular ends of the long bones.

The largest group of exostoses are those which originate at the ends of the long bones, and which are peculiar in being multiple, frequently hereditary, and often associated with abnormalities of growth. As the condition is rather one of disturbance in the process of ossification than a neoplastic process it is considered later as hereditary deforming chondrodysplasia. Other small exostoses are frequently traumatic in origin, the blow appearing to cause a displacement of cells which then take on an abnormal growth.

The *subungual exostosis* is a variety of osteoma which arises from the dorsal aspect of the terminal phalanx of the big toe. Although it does not attain to any great size it causes great pain and disability as it lifts up the nail and may erode the matrix and the soft parts. It differs from ordinary exostoses in that it forms adhesions with surrounding tissues.

The face is a not infrequent site of osteoma. The tumor may grow into the orbit, displacing the eye, or it may invade the various sinuses or the antrum of Highmore. In the peculiar and fortunately rare condition of

diffuse osteoma or lcontiasis ossea there is a diffuse overgrowth of the bones of the face, commencing in the upper jaw, and producing terrible deformity.

Osteoid-osteoma.—In 1935 Jaffe described a benign slow-growing osteogenic tumor which he named osteoid-osteoma. The tibia and femur are the bones commonly involved. The usual age incidence is 10 to 25 years. Pain is the principal complaint, with swelling and tenderness, but no heat or redness. It has generally been diagnosed as chronic osteomyelitis or abscess of the bone. The actual lesion is small, but it excites extensive formation of new bone in the surrounding tissue. At first there is proliferation only of osteoblasts, but later much intercellular substance develops which slowly becomes calcified, so that the lesion contains large patches of osteoid tissue. There is first a cellular stage, later an osteoid stage, and finally a mature stage of highly calcified atypical bone. The X ray picture presents two features: (1) the rarefied area of the tumor, (2) a surrounding sclerosis. The lesion is often wrongly labelled sclerosing non-suppurative osteomyelitis of Garré.

Chondroma.—Cartilaginous tumors of the bone occur during the growing period, and tend to cease growth when that period is over. Although occuring in bone they arise for the most part from portions of cartilage which have probably become misplaced through some error of development.

The short bones of the hands and feet are common sites of chondroma, but the tumor may occur at the ends of the long bones, the pelvis, ribs, and scapula, rarely in the skull.

Chondromata usually grow from the surface of a bone. When they arise in the interior of the bone they are known as enchondromas. Occasionally a chondroma will attain an enormous size. I have seen a cartilaginous tumor of the sternum which occupied so large a portion of the thoracic cavity that when it was removed the patient died of acute dilatation of the heart. Chondromas of the pelvis may form a most serious complication during pregnancy and parturition.

A characteristic feature is the lobulation of the surface. This is due to expansive growth from multiple centers. The tumor is, as a rule, well encapsulated and can be readily shelled out. Occasionally, however, it may encroach on surrounding tissues, and in some cases the tumor shows a curious tendency to invade the veins, travelling for a long distance along them.

Degenerative changes are frequent. The hyaline cartilage may undergo myxomatous degeneration, so that cyst-like cavities are formed containing a glairy, mucinous material. As a result, the X-ray picture may closely resemble that of giant-cell tumor of bone. In one of my specimens the lower end of the femur was hollowed out by a large central chondroma which had undergone such a degree of degeneration that it was mistaken for a giant-cell tumor. Calcification and ossification are of frequent occurrence, especially in chondromata which have ceased to grow, a condition known as ossifying chondroma. The change can readily be detected in the X-ray picture.

Chondrosarcoma is a malignant development of a chondroma. It may be easier to detect this change from the clinical behavior and the gross appearance at operation (invasion, etc.) than from the microscopic picture. In this instance the surgeon should not be persuaded against his better judgment by the pathologist's report on the section. Although the invasion of veins already referred to is most common in frank chondro-

sarcomas, yet it may occur in tumors which display no histological evidence of malignancy. In the chrondrosarcoma the regular arrangement of cartilage cells is lost, at least in parts of the tumor, and the growth is much softer and more cellular in character. Invasion of the veins is followed by distant metastases, notably in the lungs.

The condition of multiple chondromata or multiple cartilaginous exostoses, not being an example of true tumor growth, is described on page 726.

Malignant Tumors of Bone.—The classification of the primary malignant tumors of bones has always been a matter of great difficulty and complexity. A bewildering variety of names is encountered in the literature, these representing an attempt at minute subdivision. It appears very doubtful at the present time if anything is to be gained by such subdivision. In 1920 there was formed in America the Registry of Bone Sarcoma with E. A. Codman as registrar. The result was the collection of a large number of cases of malignant bone tumors with full clinical, radiological, and histological data, together with an account of the subsequent fate of the patients. A number of reviews of this material have appeared in the literature, notably those of Codman, Ewing, Kolodny, and Connor. An important contribution is the monograph by Geschickter and Copeland.

From a study of this material it becomes evident that four main types of tumor may be recognized, types which differ markedly from one another in their natural history and clinical characteristics. The recognition of these primary types is therefore of vital importance. They are: (1) osteogenic sarcoma, (2) Ewing's tumor, (3) myeloma, and (4) giant-cell tumor. From the pathological standpoint the last named is not a true malignant tumor, although in rare instances it may behave as such. It is, however, markedly destructive locally, and the clinician has to have this tumor in mind in the differential diagnosis of the first two varieties, so that it is convenient to consider it here. There is in addition a small group of unclassified and very rare tumors which will be considered separately. The secondary tumors (carcinoma) also form a separate group. Each of these main types has been much subdivided. For a fuller discussion the reader may refer to a paper by Ewing, giving the revised classification of the Bone Tumor Registry up to 1939. Of the big four by far the commonest are the first and last. From the material in the Registry, osteogenic sarcoma appears to be twice as common as giant-cell tumor. The second and third should be associated together in the mind, for they have much in common, and as they are both probably bone marrow tumors, the second may be called endothelial myeloma to distinguish it from the third or multiple myeloma.

Christensen has analyzed the age and sex incidence and the distribution of 1000 bone tumors. Osteogenic sarcoma is most common around the fifteenth year, but has been described as early as the tenth month. It is much more common in males than females. Ewing's tumor also occurs in early life, the majority of the cases appearing before the age of twenty. It also is more common in males than females. Giant-cell tumors are most common in the third decade. Osteogenic sarcoma usually occurs at the end of the long bones, giant-cell tumors in the epiphyses, Ewing's tumor in the shaft of the long bones, and multiple myeloma in the flat bones.

Osteogenic Sarcoma.—This is the most important, the most malignant,

the most common, and the most perplexing of all the tumors of bone. The term "osteogenic sarcoma," introduced by Ewing, is not intended to indicate that the tumor necessarily produces bone, although it practically always does so. It indicates that the tumor arises from cells whose function it is to form bone, but which may or may not do so.

It has been estimated that one case out of every three of sarcoma of the human body is a bone sarcoma. Commonest in the second decade of life, it is so seldom seen after the age of fifty that it is fairly safe to assume that a bone "tumor" occurring over that age must be placed in another group I have, however, seen cases over the age of sixty. The ends of the shafts of the long bones are the site of election and the most frequent site is the region of the knee. Indeed over 70 per cent of all cases of osteogenic

Fig. 460.—Osteogenic sarcoma of upper end of humerus.

sarcoma occur in the lower limb. Occasionally it commences in the middle of the shaft, so that this localization cannot be regarded as pathognomonic of Ewing's tumor, as is sometimes supposed. The principal bones affected in order of frequency are the femur, tibia, humerus (Fig. 460), pelvis, and fibula. Giant-cell tumor is common in the lower end of the radius and the lower end of the tibia, but no case of osteogenic sarcoma in these positions occurs in the Registry material. The most frequent site of all is the lower end of the femur.

A particularly interesting example of osteogenic sarcoma is a series of cases described by Martland occurring in persons exposed to radioactive influences. Of 18 girls engaged in painting the dials of watches with luminous paint who developed radiation osteitis, 5 (27 per cent) died of osteogenic sarcoma. The material was ingested in minute amounts and deposited

in the bones, which were subjected to an intense bombardment with alpha particles. Martland states that if a man has 10 micrograms of radioactive deposits in his skeleton, 370,000 alpha particles are discharged a second, each with a speed of 18,000 miles a second. In the year A.D. 3491 the bones would still be giving off 185,000 alpha particles per second. This is the first definite example of a causal agent known to produce a bone sarcoma.

The first symptom to attract the notice of the patient is pain, which may precede the appearance of a tumor by weeks or even months. This is due to involvement of the sensitive periosteum. In the later stages it may be agonizing.
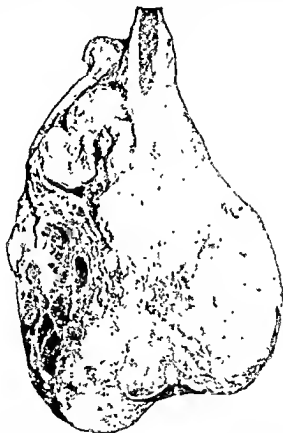
Fig. 461.—Osteogenic sarcoma of lower end of femur in a girl 10 years of age. Involvement of medullary cavity and periosteum.

Many cases give a history of trauma, although this is not so constant as in Ewing's tumor. The trauma is usually mild in character, giving rise to a contusion rather than to a fracture. In the great majority of cases the trauma merely calls the attention of the patient to a pre-existing lesion. The injury may cause hemorrhage in the tumor and thus aggravate the symptoms, including swelling. It is not possible to state that trauma can never act as a causal agent, but each supposed case should be viewed with extreme scepticism. It seems reasonable to believe that injury, especially when accompanied by hemorrhage, may accelerate the rate of growth.

Spread of the tumor takes place by the blood stream, although in exceptional cases the lymph nodes may be involved. Metastases occur

most often in the lungs. This venous invasion is due to the intimate relation which the tumor cells present to the blood vessels. They may indeed form the actual walls of the blood sinuses of the tumor. For this reason the limb must be handled with great gentleness, not only in bed but also on the operating table. The occurrence of metastases in other bones has been recorded but is very exceptional. Multiple lesions in bone suggest not osteogenic sarcoma but Ewing's tumor or multiple myeloma. As regards local extension, the spread of the tumor is limited for a time by the shell of bone. If this is destroyed by an exploratory incision for the purpose of
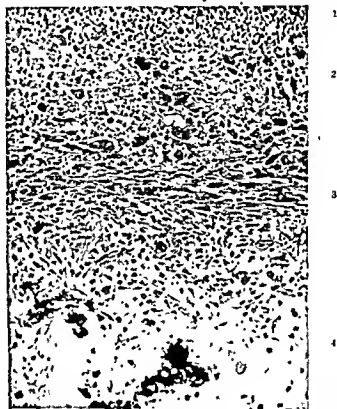
Fig. 462.—Osteogenic sarcoma. From above downward may be seen: (1) inflammatory tissue representing the ulcerated surface, (2) a zone of polyhedral and giant cells, (3) a zone of fusiform cells, and (4) osteoid tissue with commencing calcification.

a biopsy, the tumor may extend with great rapidity throughout the soft parts. The skin, although tightly stretched over the tumor, is seldom invaded or destroyed, thus differing markedly from carcinoma.

The *gross appearance* varies as do all the features of this strange tumor. The end of the shaft is occupied by a mass, which implicates the shaft, the medulla, and the periosteum, giving rise to a fusiform swelling (Fig. 461). The consistency depends on the degree of differentiation of the tumor, so that it may be hard and bony, firm and fibrous, or soft and myxomatous. Different parts of the tumor may be of varying consistency. Bluish translucent areas of cartilage may be seen here and there. A vary-

ing amount of bone is formed, sometimes almost none, sometimes large in amount. In the latter case fine spicules of bone often radiate out from the medulla at right angles to the shaft in a "sun-ray" fashion, so that the entire mass may be pervaded with spines and stalactites like "huge teeth of splintered crystal." In the vascular forms of tumor (telangiectatic sarcoma) the mass is very soft and hemorrhagic, and there may be cysts filled with blood. These tumors are usually of very rapid growth. Degenerative changes are common in bone sarcoma, as a result of which the *color may vary from fish-flesh to dark brown.* Central degeneration may lead to the formation of a cyst which may eventually penetrate the cortex. Such cysts are sometimes called malignant bone cysts. As a result of radiation treatment there may be extensive degeneration and cyst formation.
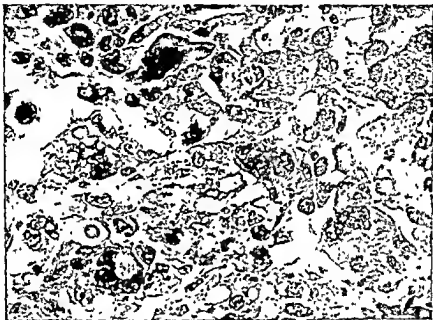
Fig. 463.—Osteogenic sarcoma. The cells vary in size and shape; there are several multinucleated tumor giant cells. × 300.

The *microscopic appearance* is probably more varied than that of any other tumor (Fig. 462). There is hardly such a thing as a typical picture. We have to consider the cells and the all-important intercellular substance. The tumor cells are osteoblasts, but these vary greatly in the degree of differentiation that they attain and in the type of intercellular material that they produce. Moreover the same variation of pleomorphism may be found in any individual tumor. This cellular pleomorphism is one of the chief characteristics of osteogenic sarcoma, and its degree is probably the best indication of the degree of malignancy. The cell type is a small spindle cell, with hyperchromatic nucleus and poorly defined cell borders. There is no such thing as a round-cell sarcoma of bone. The round-cell tumors are those of the marrow, namely Ewing's tumor and multiple myeloma. There may be large spindle cells, thicker and plumper, with elongated processes. There may be still larger polyhedral cells. The nuclei of all these cells are hyperchromatic, and mitoses are usually num-

erous. Finally there are often giant cells. These are of two types, tumor giant cells and foreign body giant cells of the epulis type, similar to those seen in tuberculosis and in a giant-cell tumor. The tumor giant cells are usually mononuclear, but they may contain a small number of hyperchromatic nuclei (Fig. 463). The foreign body giant cells contain large numbers of nuclei scattered throughout the cytoplasm. They appear where there is much bone destruction, and especially where an exploratory operation has been done previously. There is something much more irregular, atypical, and neoplastic about a tumor giant cell than a foreign body giant cell.

But the characteristic feature of an osteogenic sarcoma is not its cells but the intercellular substance which they produce. This may take any of five forms: Hyaline and fibrous, cartilaginous, myxomatous, osteoid, and
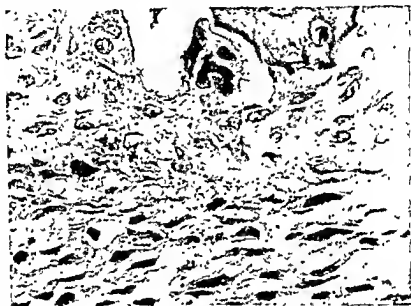
Fig. 464.—Osteogenic sarcoma of bone. New bone formation in upper part of section. × 700.

osseous. Frequently more than one of these is present. The hyaline and fibrous stroma is the most common. It varies in amount, being extremely abundant in the so-called sclerosing form of osteogenic sarcoma. Myxomatous material is usually the result of the degeneration of a cartilaginous matrix. Lime salts can be recognized by the dark blue color with hematoxylin staining as well as by the effect on the knife. The bone tissue is usually laid down in the form of radiating spicules at right angles to the shaft. The reason for this probably lies in the fact that osteoid tissue formation and ossification tend to follow the line of the blood vessels, and as the tumor pushes the periosteum in front of it, the vessels passing from the periosteum to bone are stretched in a direction at right angles to the shaft. It is important for the pathologist to distinguish between tumor bone and true bone. Tumor bone looks atypical and imperfectly

formed, it blends with the stroma of the tumor, and it presents no bordering line of osteoblasts (Fig. 464).

The variations in the nature of the matrix have been used in the past as a basis for further subdividing bone sarcoma. Thus we hear of osteochondrosarcoma, osteochondromyxosarcoma, and so on. From what has already been said it is evident that such a classification is meaningless and useless. These variations in the stroma do not affect the natural history of the disease nor the prognosis for the patient.

The vessels of the tumor are of great importance. Usually, they are numerous. In the cartilaginous form they are scanty. When very abundant, the tumor is said to be of the telangiectatic type. In some places the tumor cells replace the endothelium and actually form a lining for the vessel, a striking peculiarity the importance of which in rela-

Fig. 465.—Osteogenic sarcoma of humerus with complete destruction of bone.

Fig. 466.—Osteogenic sarcoma of lower end of femur.

tion to the early occurrence of pulmonary metastases at once becomes evident. Such vessels must be formed by the sprouting of a column of tumor cells. The limb must therefore be handled with great gentleness. It is easy for metastases to be set up at the time of operation. Preliminary radiation of the tumor by closing the vessels diminishes this danger to a considerable degree.

The X-ray picture should always be taken in conjunction with the gross and microscopic appearance (Fig. 465). Codman in an article of great value on the diagnosis of osteogenic sarcoma gives five main radio-

logical points. (1) Combined central and subperiosteal involvement (Fig. 466). Benign tumors are either inside or outside the old cortex; malignant tumors are both. At the extreme margin of the tumor there is a little lip of reactive bone which represents the last line of defense of normal osteoblasts retreating in circular formation as the tumor advances under the periosteum (Codman). (2) Presence of the old shaft. The shaft, although permeated by the tumor, is not displaced. In giant-cell tumor the shaft is destroyed, and in Ewing's tumor it is greatly thickened. (3) Invasive character. The edge is irregular, never rounded and smooth as in giant-cell tumors. (4) Osteolytic and osteoblastic. In the great majority of cases there is both bone destruction and bone formation. Bone formation usually takes the form of radiating spicules (sunray appearance), but this is by no means constant. (5) Involvement of the soft parts.

As already indicated, the osteogenic sarcomas have been divided into a number of subgroups. The Registry, and Ewing in his text-book, recognize four types: (1) periosteal, (2) medullary and subperiosteal, (3) sclerosing, and (4) telangiectatic. This division is based on gross characteristics. The varying miscoscopic appearance has also been used, so that we have a number of osteosarcomas, myxochondrosarcomas, etc. To the writer it appears that, whilst a minute study of individual tumors is of the utmost importance, recent gains in knowledge have been largely in the direction of dividing the malignant tumors of bone into certain great classes of genera, each of which displays a characteristic natural history, and that undue subdivision and differentiation is apt to obscure the importance of these great groups.

Prognosis.—The prognosis of osteogenic sarcoma is extremely grave but not necessarily hopeless. In 1935 there were 74 cases of so-called five-year cures in the Bone Registry material. The youth of the patient is a bad feature; as a rule, the younger the patient the more rapid the growth. Extreme vascularity is a dangerous sign; in these cases pulmonary metastases are frequent and early. Numerous mitoses and marked pleomorphism are unfavorable features. For the present, however, our knowledge is not sufficient to allow us to give a really reliable prognosis.

Ewing's Tumor.—It was in 1920 that Ewing began to separate from the general mass of malignant bone tumors one which he considered to be an endothelioma, and which has been variously named endothelioma of bone, endothelial myeloma, Ewing's sarcoma, and Ewing's tumor. As there is no unanimity as to the exact nature of the condition, the last name appears to the writer the most suitable for the present. The clinical history is characteristic. Indeed the diagnosis can sometimes be made more readily from the history and the radiological picture than by the microscopic examination of an excised piece of tissue.

It is a disease of the young, just as the rather similar multiple myeloma is a disease of middle age. Over 80 per cent of the cases occur before the age of 30, and the majority occur between 5 and 15. There is often a history of trauma. This is shortly followed by the occurrence of pain, at first intermittent, but later continuous. A swelling appears. There may be some fever. When the swelling is incised a soft diffluent material is obtained, following which the tumor is likely to increase rapidly in size, with the discharge of a pus-like material through the incision. It will be

appreciated how readily such a condition may be mistaken for osteomyelitis. In two cases which I studied this mistake was made in both instances. The following is a characteristic history of a case studied in my department in Winnipeg and published by Pritchard. A girl of 18 fell on her arm while skating. The injury was followed by attacks of pain, separated at first by intervals, and accompanied by fever and the development of a swelling at the site of injury. The pain and fever became constant and continued for months. The roentgenogram showed diffuse widespread involvement of the shaft of the humerus, as well as lesions in the ilium and skull.

Fig. 467 —Ewing's tumor of humerus.

Fig. 468.—Ewing's tumor of humerus. The growth is characteristically diffuse, involving the entire shaft. There were secondary growths in several other bones.

At autopsy soft breaking down tumors were found in the humerus, spine, sternum, ilium, and skull.

The *X-ray picture* is characteristic. The greater part of the shaft is involved, as compared with the localization of an osteogenic sarcoma in one end of the bone, the marrow cavity is widened, and there is widespread destruction of bone out as far as the periosteum. No new bone is formed by the tumor, it is not osteogenic, but there may be a periosteal reaction formation of new bone at the periphery (Fig. 467). A characteristic longitudinal striation of the bone may be observed, as if the tumor had separated the shaft into laminae. The general picture is one of bone absorption.

The disease usually commences in one of the long bones (Fig. 468), most commonly in the tibia, humerus, femur, fibula, and clavicle in that order of frequency. Of the small bones the os calcis is most often involved. One of my cases was regarded as an osteomyelitis of the os calcis until a pathological fracture of the femur some months later revealed the true nature of the condition (Fig. 469). The tumor, which commences in the medullary cavity, is very soft, and may resemble brain tissue or red jelly. Having destroyed the shaft of the bone it invades the surrounding soft parts

The *microscopic* picture may be obscured by a marked tendency to degeneration and softening, by previous radiation, or by faulty fixation. Under these circumstances the cells may appear to be round, but in fresh

Fig. 469.—Ewing's tumor of os calcis showing characteristic destruction of the body, whilst the epiphysis is spared.

and perfectly fixed material they are seen to be polyhedral. The nuclei are small and round, often rather washed out in appearance and lacking the character and chromatin of the nuclei in multiple myeloma which are usually hyperchromatic. The cells may be arranged in sheets, or they may line vascular channels, in which case they may be elongated. There may be a perithelial arrangement around these channels. Sometimes the cells are grouped to form pseudorosettes, which has led to the suggestion, probably on insufficient grounds, that many of these tumors are really examples of secondary neuroblastoma rather than primary bone tumors (Willis). The cells apparently form no intercellular substance, in striking contrast to those of an osteogenic sarcoma (Fig. 470).

As to the origin and nature of the tumor there have been wide differences of opinion. Reticulum-cell sarcoma, lymphosarcoma, and round-cell

sarcoma of undifferentiated mesenchymal cells have all been suggested. The histological evidence appears to support Ewing's original suggestion that the tumor is a diffuse endothelioma of vascular (blood or lymphatic) origin.

One of the most important features of the tumor is its tendency to set up metastases in other bones. In those cases which come to autopsy the skull is practically always involved. In my own case referred to above there were secondary growths in the skull, sternum, vertebrae, and ilium. These secondary tumors do not develop for some time after the appearance of the initial lesion, thus differing from multiple myeloma, the other malignant bone tumor in which a number of bones are involved. Secondary growths in the lungs are commonly found at autopsy, and more rarely there may be tumors in other internal organs.

A characteristic feature of the disease, which Ewing used in the initial differentiation of the condition, is the remarkable reaction to radiation. As the result of this treatment the tumor may be seen to melt away for a time in a manner never observed in osteogenic sarcoma. This reaction is of great diagnostic value, and is greatly to be preferred to a biopsy, a procedure merely calculated to stimulate the growth of the tumor. In time the tumor tends to recur, but the prognosis, although undoubtedly grave, is certainly better than that of myeloma or osteogenic sarcoma. Some cases treated by early amputation have made long recoveries, and even when metastasis to other bones has occurred, the disease has been held in check by radiation for a number of years. In the majority of the cases in the Registry, however, death has occurred within two years.

Fig. 470.—Ewing's tumor. × 500.

Willis points out that widespread metastatic carcinoma of bone may give a picture exactly like that of Ewing's tumor, and that in many of the reported examples of the latter condition only biopsy has been done, but no subsequent autopsy. This is a very important point which has been generally overlooked, and it is not too much to say that a diagnosis of Ewing's tumor must be confirmed in every case by autopsy with the exclusion of the possibility of some latent carcinoma before it can be accepted.

Multiple Myeloma.—This is the rarest of the four main types of primary malignant bone tumor. Like Ewing's tumor, it is a disease of the bone marrow. The age incidence, however, is different, for 80 per cent of the cases occur after the age of forty. It is twice as common in males as in females. Pain is an outstanding feature. It often begins in the back in the lumbar and sacral regions, and may at first be vague and indefinite.

After the initial attack there is usually no pain for several months, but in the final stages the pain is often agonizing. The average duration of the disease is from one to two years.

The most striking feature of the morbid anatomy is multiplicity. It is impossible to be certain whether the initial lesion is a local one with the early formation of multiple metastases, or whether the disease commences simultaneously in a number of bones. The bones of the thoracic cage are those most frequently involved, that is to say the sternum, ribs, and vertebrae. These are all red marrow bones. The skull (Fig. 471), pelvic bones,

Fig. 471.—Multiple myelomata in the skull.

and clavicle come next in order of frequency; then the long bones of the limbs.

The tumors in the marrow vary in size from that of a pea to that of an orange. They are much more circumscribed than the lesions of Ewing's tumor, but later they may become diffuse throughout the length of the shaft (Fig. 472). There is no bone formation, merely destruction, so that pathological fracture is commoner than in any other bone tumor. The marrow cavity is expanded and filled with a soft grey or red mass, and the cortex greatly thinned. In advanced cases the rarefaction is so great that the bone can be cut with the greatest ease.

The *microscopic picture* shows rounded cells arranged quite diffusely with no intercellular substance. The type of cell varies somewhat in different cases. Indeed four varieties are described, which are supposed to arise from a plasma cell, a lymphocyte (Fig. 473), a myelocyte, and a nucleated red blood cell. In the majority of cases the tumor is composed of cells closely resembling plasma cells, rounded or polygonal, and with an eccentric nucleus (Fig. 474). Many of the cells may contain two or even three nuclei, these cells being rather larger than their neighbors. Although the picture is a little more pleomorphic than that of Ewing's tumor, it has none of the marked pleomorphism of the osteogenic sarcoma. There is much doubt regarding the cell of origin. For the present it appears best to regard multiple myeloma as a bone marrow tumor. Jackson and his associates consider the condition as a disease of the blood-forming organs like leukemia, for the lymph nodes as well as the marrow may be involved. This is best seen in the plasma cell type (plasmacytoma) which may start in bone and spread later to lymph nodes, or may start in lymph nodes and spread to bone. In rare cases the blood contains plasma cells.

Fig 472.—Multiple-myeloma. Numerous punched out cavities in shaft of humerus.(Kindness of Dr.H.M.Vango.)

The *X-ray picture* is characteristic, and from it the diagnosis can readily be made. The radiograph shows numerous, rounded, punched-out areas of varying size in more than one bone (Fig. 475). The ribs present a mottled appearance. The skull is not thickened, and may be full of sharply defined holes. Pathological fractures are common. There is no new bone formation.

Radiation produces much the same effect on myeloma as it does on Ewing's tumor, causing the nodules to melt away. The effect, however, is less lasting, and recurrence takes place after a short time.

Metastases in the internal organs may occur but are not common. The liver and spleen are the chief sufferers. The lungs are almost never involved. Apart from the presence of metastases the spleen is often moderately enlarged. In one case which I examined at autopsy it weighed 750 grams.

The presence of a peculiar albumose in the urine was described by Bence-Jones as long ago as 1845. It appears as a cloud when the urine is heated to 55° C., disappears at 85°, but reappears on cooling. Bence-Jones albumosuria occurs in less than 50 per cent of the cases, so that its absence does not mean much. Extract of bone marrow has properties identical with Bence-Jones protein, and when this extract is injected into rabbits the protein appears in the urine. It is probably produced from leucocytes and other marrow cells, thus explaining why it is sometimes found in

24

leukemia and in secondary carcinoma of bone marrow. Renal failure is common in the advanced stages, due to casts of Bence-Jones protein which
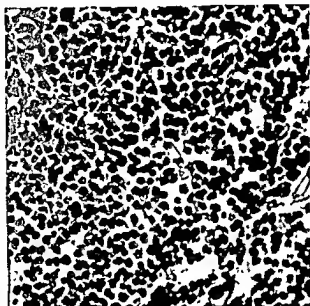
Fig. 473.—Multiple myeloma in vertebra. Cells are of the lymphocyte type. × 300.
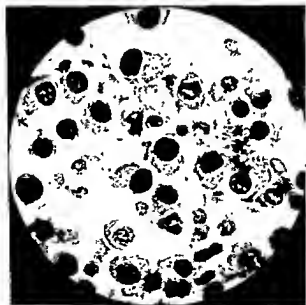
Fig. 474.—Multiple myeloma The cells, polyhedral in form and with eccentric nucleus, are of the plasma cell type. × 800.

obstruct the tubules. Owing to replacement of the red marrow by tumor tissue a marked secondary anemia gradually develops.

Hyperproteinemia occurs in many cases (25 to 45 per cent). In nearly every case the albumin value is low and the globulin greatly raised. Bence-Jones protein may form an important part of the total plasma protein, though cases with Bence-Jones protein in the urine are likely to have normal blood protein, and those with high blood protein usually have little or no Bence-Jones protein in the urine. It has been suggested that destruction of the bone marrow by the tumors is responsible for the excess blood protein.

Amyloid disease occurs in about 25 per cent of the cases. The amyloid is generally in unusual sites such as the intestine, voluntary muscle and bone, whilst the spleen, liver and kidney are often not involved. It can be shown experimentally that amyloid may be formed as the result of an acquired hypersensitivity to abnormal protein, and that may be the explanation in this case.

Giant-cell Tumor (Osteoclastoma).— This tumor was formerly known as giant-cell sarcoma and myeloid sarcoma under the mistaken belief that it was malignant. It is locally destructive, but does not give rise to metastases, although there is a tendency to recurrence. In a few rare cases a malignant (sarcomatous) transformation occurs with spread to the blood stream and the formation of metastases in the lungs. Some of these cases must be accepted with reserve, as they may have been examples of bone sarcoma from the beginning. Others are undoubtedly examples of malignant change in a giant-cell tumor.

The tumor develops in children and young adults, usually before the age of thirty years. The common site is at the ends of the long bones, either epiphysis or metaphysis, especially the lower end of femur and upper end of tibia. These tumors also occur in the maxillae, vertebral column, tendon sheaths, bursae, and the capsule of joints. Giant-cell tumors occur in osteitis fibrosa cystica, often originating in the wall of one of the cysts. The tumor may be periosteal or medullary in type. The former occurs in the maxillae, and constitutes the commonest form of *epulis*.

Fig. 475.—Multiple myeloma. The femur is studded with tumor nodules.

The *gross appearance* is that of a soft, dark-red or maroon-colored hemorrhagic mass, sometimes presenting yellow areas. The center of the bone is expanded, and the cortex often reduced to a mere shell (Fig. 476), so that spontaneous (pathological) fracture may first draw attention to the existence of the lesion. When the expanded but greatly thinned bone is palpated the sensation known as eggshell crackling may be experienced by the surgeon. Trabeculae of bone are left traversing the cystic lesion

like beams supporting a crumbling building. This appearance is well seen in the macerated specimen, and even better in the X-ray film, where the lesion has a multicystic character which has been likened to soap-bubbles, with sharp limitation from the surrounding bone (Fig. 477). The only other lesion with which this picture could be confused is enchondroma of bone.

Microscopically the tumor is composed of three types of cells: spindle-shaped cells, round cells and giant cells (Fig. 478). The round cells are more numerous during the period of active growth. Predominance of the fusiform cells indicates quiescence of the growth and a tendency to heal-

Fig. 476.—Giant-cell tumor of bone.

Fig. 477.—Giant-cell tumor of upper end of tibia. The multicystic appearance and the sharp limitation of the growth with complete absence of infiltration are well shown.

ing; they are the main constituent of the lesion in osteitis fibrosa. Giant-cell tumor of the vertebrae, which responds very favorably to even partial removal, is composed largely of spindle cells. The giant cells are large, multinucleated cells of the osteoclast type. They may be very numerous in one part, scanty or absent in another, so that a number of sections may have to be examined. They have the general characteristics of foreign body giant cells. They possess numerous small oval nuclei, which are situated towards the center of the cell, not around the periphery or at one end as is so commonly seen in tuberculosis. The tumor is highly vascular, so that hemorrhage is frequent.

The *epulis* (*epoulis*, upon the gums) is a tumor in the gum growing in relation to the teeth. There are two forms: the giant-cell epulis, which

is the common type and is similar in nature to the giant-cell tumors of bone, and the fibrous epulis which is similar in character to osteitis fibrosa. Epulides occur in children and young adults, and arise from the alveolar dental periosteum of the deciduous teeth (canine and biscuspids). They hardly ever occur at the site of the molars, which make only one (permanent) appearance. The growth is outward, often between the teeth, and does not invade the bone. In addition to the epulis, a central giant-cell tumor of bone may occur in the lower jaw between the symphysis and the mental foramen.

The *nature of the giant-cell tumor* has long been a matter of dispute. By some it is considered to be inflammatory rather than neoplastic in nature, the giant cells being regarded as foreign body giant cells. The most satisfactory way of regarding the lesion, as suggested by Geschickter
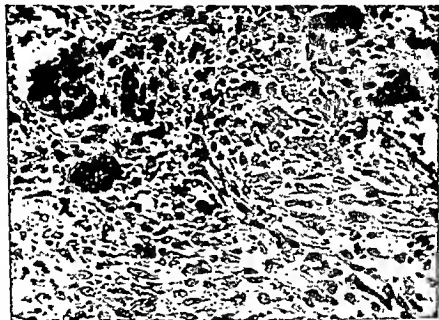
Fig. 478.—Giant-cell tumor of head of tibia. Both the fusiform cells and the multi-nucleated giant cells are abundant. × 325.

and Copeland, is to consider giant-cell tumor and osteitis fibrosa as two phases of a transition process in the histogenesis of permanent bone; the former is an active vascularizing phase, the latter a healing phase. In the formation of normal bone there is a canalization, vascularization, and finally removal of calcified cartilage, a process in which osteoclasts and round and spindle cells similar to those of the giant-cell tumor play an active part. This process may overstep the bounds of normal activity and become neoplastic, giving rise to a tumor which may be called an *osteoclastoma*. If the process is restrained and only slightly destructive, the result will be localized osteitis fibrosa with the possible formation of a bone cyst. Trauma is probably a factor of importance in disturbing the blood supply to the growing part, but the relation of trauma to a tumor must always be subjected to critical scrutiny.

This view throws light on a number of the features of giant-cell tumor.

It explains its age incidence, its localization at the growing ends of bones (including the epiphysis), and its relation to osteitis fibrosa. The giant-cell epulis arises in a similar manner. The shedding of the deciduous teeth is brought about by the action of giant-cell odontoclasts, and the tumor is an *odontoclastoma*. The fibrous epulis corresponds to osteitis fibrosa. In the skull giant-cell tumors of central character, as distinguished from the epulides, are confined to parts developed in cartilage, *i. e.*, temporal fossa, the part of the mandible between the symphysis and mental foramen which is developed from Meckel's cartilage, and the anterior part of the superior maxilla. The giant-cell tumors (xanthomas) of tendon sheaths may also be explained in this way. The calcified structures with the removal of which they are concerned are the sesamoid bones.

Stewart and others believe that the two processes are entirely distinct, and that the true osteoclastoma is a primary neoplasm unrelated to osteitis fibrosa. It is more sharply circumscribed than the giant-cell lesions of osteitis fibrosa and the rest of the skeleton is quite normal. The rare cases of malignant giant-cell tumor would rather support this view.

Unclassified Sarcomas.—It is not possible to pigeonhole every malignant tumor of bone in one of the great groups just described. Rare cases occur which refuse to go into these groups. Of these, two of the best recognized are the extraperiosteal fibrosarcoma and the angio-endothelioma.

Extraperiosteal Fibrosarcoma.—This appears to be a very rare tumor of which there are few examples either in the literature or in the Registry. It is the same as the periosteal fibrosarcoma, arising from the outer, fibrous non-bone-forming layer of the periosteum. The tumor is therefore an ordinary fibrosarcoma and is not osteogenic. It is firm and white, and does not invade the bone, although it may erode it slightly from pressure (Fig. 479). Microscopically it consists of spindle cells separated by fibrillar intercellular tissue. It is of lower malignancy than the osteogenic sarcoma, and the cures of "bone sarcoma" reported as the result of amputation are largely recruited from this class.

Reticulum-cell Sarcoma.—In 1939 Parker and Jackson described a form of bone sarcoma composed of cells similar to those of reticulum-cell sarcoma of lymph nodes. In the past it has been mistaken for Ewing's tumor, and less frequently for other forms of bone sarcoma. The majority of cases appear before the age of 40, and many before the age of 20. The physical condition is far better than would be expected from the size of the lesion, and in no other bone tumor may the lesion be so extensive and at the same time so amenable to appropriate treatment (radiation followed by amputation). The usual X-ray picture is one of bone destruction, and fracture is common. The tumor occurs principally in the long bones, but it also occurs in the flat bones and spine. The cells are large with abundant cytoplasm which may show evidence of ameboid activity in the form of pseudopodia. The nuclear outline is indented or reniform. With a silver stain a delicate reticulum is seen to encircle single cells, thus distinguishing the lesion from Ewing's tumor, in which the reticulum surrounds groups of rather smaller cells. The ameboid cells and the arrangement of the reticulum are the characteristic features.

Angio-endothelioma.—This tumor is even more rare, there being only two cases in the Registry. Clinically it is likely to be mistaken for osteogenic sarcoma, whilst histologically it may be mistaken for secondary carcinoma. Neither the clinical nor the radiological features are characteristic. The disease ends fatally from pulmonary metastases. The tumor cells, which appear to arise from vascular endothelium, may resemble carcinoma cells. They are arranged in alveoli and tubules, some of which contain blood, but others are filled with tumor cells. Kolodny has made a special study of these tumors.

Liposarcoma of Bone.—A very rare form of bone tumor is liposarcoma, which arises from the lipoblasts of the marrow. The tumor is soft, yellow in color, and may be multiple in bone. Whether this represents multiple primary origin or metastases is not certain. It is extremely cellular, the cells being large, arranged loosely or in alveolar groups, and have an abundant cytoplasm filled with fine droplets of fat (Fig. 480). On this account the lesion may be confused with secondary hypernephroma. The tumor grows

slowly, and the duration of life is to be measured in years rather than months. It is radiosensitive.

Solitary Plasmacytoma.—This is a rare tumor which may occur primarily in bone or in the upper air passages. According to Willis, only 14 cases have been reported in bone. As a rule it is of only local malignancy, and is amenable to local removal. It is probably a distinct entity and not merely an early localized stage of multiple myelomata.

The Diagnosis of Bone Sarcomas.—It has been the usual practice in cases of bone tumor the nature of which was in doubt to excise a small

portion for microscopic examination. It is well that the surgeon should recognize the pitfalls of this procedure. An atypical piece may be removed or one which is gravely altered by inflammatory or degenerative changes. This is more true of bone sarcomas than of tumors of other tissues owing to the confusing variety of histological features which they may present. In this more than in any other field of microscopic diagnosis it is essential to take all the clinical

Fig. 479.—Extraperiosteal fibrosarcoma of the tibia. The cortex of the bone is quite intact.
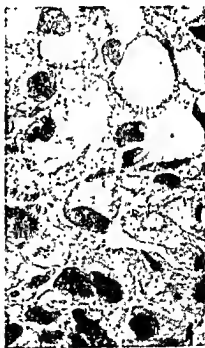
Fig. 480.—Liposarcoma of bone. × 500.

facts into consideration. Even an observer of such wide experience as Professor Ewing remarks that "the more experienced the pathologist, the more he learns to rely on clinical data for clinical diagnosis, and the more he urges the surgeon to make his diagnosis on clinical observation, and not to expect too much from the study of small pieces of tissue."

A diagnostic incision of a malignant bone tumor is not without its

dangers in the matter of dissemination. If a giant-cell tumor is to be treated by radiation it is very important that the skin and the tumor capsule should not be incised for diagnosis, for the scar may break down under repeated radiation, and infection of the tumor may result.

The use of the X-ray has placed in the hands of the surgeon a potent means of diagnosis. The therapeutic test affords conclusive evidence of the nature of certain tumors of bone. Myelomas and diffuse endotheliomas in particular melt away under radiation. The giant-cell tumor is affected more slowly, but the growth is held in control, and the shaft gradually restored. Osteogenic sarcomas do not respond to radiation.

With regard to the X-ray picture, Ewing summarizes the matter as follows: "Osteogenic sarcoma almost never affects the middle half of the shaft, but is a disease of diaphyseal ends; erosion or destruction of a seg-

Fig. 481.—Metastatic carcinoma of prostate in spine.

Fig. 482.—Carcinoma destroying bone, three osteoclasts. × 500.

ment of shaft is nearly constant in osteogenic sarcoma; the benign central tumors regularly widen the shaft and displace the periosteum with its thin shell of bone, long before more aggressive forms of this disease invade the soft tissue; the myelomas and diffuse endotheliomas involve wide segments of the bone, often the midportions, and cause smooth gradual fading of the shaft. Syphilis, tuberculosis, chronic osteomyelitis and periostitis, and Paget's disease, each presents its own peculiar morphology and clinical setting, and, with rare exceptions, lacks the specific features of bone tumors. It must be admitted that these interpretations require experience; but no inexperienced person should undertake to deal with bone

tumors. When the experienced observer is unable to reach a conclusion, then resort must be made to the diagnostic incision before amputation is advised."

Secondary Carcinoma.—Metastatic tumors in bone from a primary glandular carcinoma are common. The secondary growths are usually multiple (Fig. 481), sometimes to the extent of a real carcinomatosis of the skeleton, but in the case of hypernephroma the metastasis is said to be single in over 50 per cent of cases, so that the advisability of removing the

Fig. 483.—Carcinomatous deposit in left humerus secondary to carcinoma of breast.
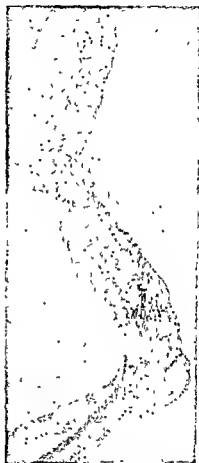
Fig. 484.—Right humerus almost entirely replaced by carcinomatous growth secondary to carcinoma of breast. *Pathological fracture.*

bone tumor may be considered. The prostate is the most common source of skeletal metastases, with breast second, kidney third, and stomach, lung and thyroid less common and in that order. The size of the tumor is no index of the probability of metastases. I have seen secondary involvement of the spine, so extensive and deforming as to be mistaken for Pott's disease, originate from a carcinoma of the breast which could not be detected until the breast was incised at autopsy. Metastases may appear long after operation on the primary tumor, Geschickter and Maseritz citing

a case where the interval was 18 years. The order of frequency of involvement in the case of the breast are spine, pelvis, femur, skull, ribs, humerus; in the prostate, pelvis, vertebrae and femur; in hypernephroma, humerus, spine, femur, pelvis, ribs, skull and sternum. Malignant melanoma may cause widespread metastases throughout the skeleton.

The lesion in the bone is usually osteolytic (Fig. 482), but osteoplastic changes may also be present. These changes are best seen in the X-ray picture (Figs 483 and 484). In hypernephroma the lesion is purely osteolytic. In breast cancer it is mainly osteolytic, but osteoplastic changes may be added. In cancer of the prostate the bone lesions are characteristically osteoplastic, the tumor being surrounded by and interspersed with marked new bone formation. In spite of these changes fracture may occur. Even in markedly osteolytic lesions satisfactory healing of fractures is common. In the prostatic cases extensive formation of new bone may obliterate the
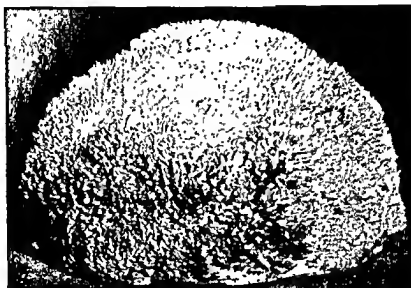
Fig. 485.—Metastases in skull from neuroblastoma of adrenal medulla.

marrow cavity and give rise to severe anemia. It is the red marrow bones which are the chief sites of metastases, including the upper end of the femur and humerus. Cancer of the thyroid may give rise to the formation of large tumors in the vault of the cranium. Neuroblastoma of the adrenal medulla, a rare tumor of young children, metastasizes to the cranium, particularly the orbit; it excites a remarkable and characteristic formation of periosteal new bone, mainly in the form of spicules (Fig. 485). Metastases in the spine spare the intervertebral discs in contrast with the marked destruction seen in Pott's disease, but, unfortunately, this is not an invariable rule.

The *blood picture* in carcinomatosis of bone may be so characteristic as to be of diagnostic value, though in other cases it may be normal. Extensive replacement of the red marrow tends to leuco-erythroblastic anemia, *i. e.*, an anemia characterized by the presence of immature white and red cells. The anemia is usually hypochromic in type and not neces-

sarily severe. The young red cells are reticulocytes and erythroblasts; the white cells show a "shift to the left" and occasional myelocytes. There may be a moderate leucocytosis owing to stimulation of the remaining normal marrow, but often this is apparent rather than real, the nucleated red cells being mistaken in the counting chamber for white cells.

Bone may become involved in a carcinomatous process through spread of the disease from the adjacent soft parts. Carcinoma of the mucous membrane of the mouth may invade the jaw or the palate. Or carcinoma may commence in a sinus communicating with bone, and eventually the bone itself.

Fibromas of bone are usually found in connection with the bones of the face, especially the superior maxilla. The tumor may form a nasopharyngeal polypus with ulceration of the mucosa. It grows from the periosteum.

Angiomas have on rare occasions been found in the vertebrae, the skull, and the sternum

Skeletal Lipoid Granulomatosis.

Disturbances of lipoid metabolism may be accompanied by storage of lipoid in the tissues (lipoid histiocytosis). This is seen in Gaucher's disease (storage of lipoprotein of cerebroside type), in Niemann-Pick's disease (storage of phosphatide lipoid), in Tay-Sach's disease (storage of cerebroside protein), and in Schüller-Christian's disease (storage of cholesterol). *Schuller-Christian's disease* is a manifestation of what Fraser calls skeletal lipoid granulomatosis. Hypercholesterolemia is constant, and the excess lipoid is taken up by cells of the histiocyte type. The lesions are firm and putty-like, and may be yellowish in color. The chief sites in order of frequency are the dura of the base of the skull with extension into the sella turcica and pressure on the pituitary with accompanying pituitary insufficiency (infantilism and the adiposogenital syndrome), the subcalvarial dura, the mastoid air-sinus, the clavicle, ribs, vertebrae, and long bones. Extension from the base of the skull through the supraorbital fissure into the orbit causes marked proptosis. The new tissue formation leads to extensive decalcification and characteristic defects in the skull and other bones seen in X-ray films.

The first *histological change* is swelling and proliferation of the endothelial cells lining the capillaries owing to accumulation of lipoid. Histiocytes (mononuclears) are filled with lipoid, and fuse to form multinucleated giant cells. These cells break down and liberate their lipoid. Masses of new granulation tissue are formed in response to the lipoid irritant. Deep radio therapy destroys the lipoid-filled histiocytes, and the lesion becomes fibrosed and finally recalcified.

OSTEITIS FIBROSA

This condition was first described by von Recklinghausen in 1891, and is sometimes known as von Recklinghausen's disease, not to be confused with the commoner multiple fibromatosis of cutaneous nerves which bears the same name. For long it was considered to be a form of chronic inflammation of bone, as indicated by the name osteitis. It is now known that in the majority if not in all cases the disease is a manifestation of hyperparathyroidism, a result of overactivity of the parathyroid glands due either to tumor formation or to hyperplasia. As long ago as 1904 Askanazy noticed a relationship between parathyroid hyperplasia and generalized

osteitis fibrosa, and in 1907 Erdheim pointed out that parathyroid hyperplasia was common in osteitis fibrosa and in osteomalacia, but our modern and more accurate knowledge of the subject is largely due to the work of Donald Hunter, whose papers should be read by anyone interested in the subject.

The skeletal changes and the changes in the blood chemistry are exactly the same as those produced by the continued administration of parathyroid extract. The essential bony change is a generalized decalcification and rarefaction (Fig. 486) accompanied by the formation of a cellular connective tissue as described below. The biochemical changes are equally striking and even more characteristic. The calcium which is extracted from

Fig. 486.—General and marked decalcification of the skeleton in hyperparathyroidism (From Boyd, Pathology of Internal Diseases, Lea and Febiger, Publisher.)

the bones by the increased production of parathormone appears in the blood in large amount, and the *serum calcium* rises from the normal figure of 10 mg. per 100 c.c. to 15 or 20 mg. The serum phosphorus, on the other hand, falls below normal; this fall is even more significant than the rise in the calcium. The *plasma phosphatase*, an enzyme produced by the osteoblasts and intimately concerned with the formation of bone, is considerably raised. It is of interest to note in this connection that the fractures which so frequently occur in the rarefied bones heal with remarkable readiness. Removal of the enlarged parathyroid (more than one gland may be involved) is followed by an immediate fall in the blood calcium. So great may be this fall that there may be a danger of the development of tetany. There is an associated improvement in the skeletal condition.

and a cripple has been known to throw away his crutches. Much of the calcium which is removed from the bones is excreted in the urine so that there is a negative calcium balance. Some of it may be deposited in the renal pelvis to form a calculus, and some in the walls of the arteries. These are examples of *metastatic calcification*.

Clinical Features.—The disease is essentially one of early life. Most of the cases occur between the ages of 10 and 20, but in Bloodgood's series one patient was only 2½ years old. Cases after the age of 20 are almost unknown, and if occurring later in life are likely to be examples of Paget's disease or osteomalacia.

The symptoms are by no means proportionate to the degree of bony change. Of the three principal symptoms—pain, swelling, and fracture—pain is rarely a prominent feature and the swelling occurs late. Very many

Fig. 487.—Osteitis fibrosa cystica; replacement of bone by fibrous tissue. × 60.

patients come for the first time complaining of spontaneous fractures. Owing to the softening of the bones which are very poor in lime there may be bowing of the arms and legs, and these deformities are often very angular and irregular. The bones most commonly affected are the humerus, the femur, and the tibia in the order named. The jaw, the skull, and the bones of the trunk may occasionally be involved.

The X-ray picture of the cysts is very striking. The clear area is often continued down the shaft as a pointed extension; in other bone cysts, such as those which occur in giant-cell tumors, the lower limit is rounded. Widespread rarefaction of the bones is apparent in the more advanced stages.

The important changes in blood chemistry, on which the clinical diagnosis is ultimately based, have already been described.

Morbid Anatomy.—The medullary tissue is replaced by new connective tissue with or without cyst formation. It is important to note that

the cyst formation, the dramatic feature of the disease, is by no means essential. In this respect the condition resembles the so-called multiple cartilaginous exostoses in which the development of exostoses is interesting but incidental.

The main pathological features are a general and diffuse degeneration and absorption of bone, a growth of vascular connective tissue (Fig. 487), cyst formation, the rather frequent development of giant-cell tumors, and spontaneous fractures. The cysts are usually small, but may attain a considerable size. The wall of the cyst may become greatly thinned, and in the case figured in the text it was in places thin as parchment, so that the slightest trauma was sufficient to produce a fracture. The cysts are lined by fibrous tissue. The fluid contents of the cysts are never distinctly hemorrhagic; they are usually thin, dark brown in color, and show a few blood cells microscopically. Frequently, however, the cysts are filled with gelatinous or fibrous masses rather than with fluid.

The bones are remarkably porous, so that curvatures and angular deformities are fairly common. Sections of the bone show a bony meshwork enclosing vascular marrow-like tissue. The compact bone may have largely disappeared.

In a considerable number of cases osteitis fibrosa is complicated by the development of a benign giant-cell tumor (Fig. 488). Giant cells are found even more frequently in the walls of the cysts and in the new connective tissue. The giant-cell tumors may be quite minute or may be large enough to be detected clinically. They apparently represent a foreign body reaction in response to the destruction of bone. The patient may die of osteogenic sarcoma (Fig. 489), but this tendency is not nearly so marked as in Paget's disease.

Fig. 488.—Giant cells in osteitis fibrosa. × 150.

The *localized form* of osteitis fibrosa is much more common than the generalized disease and bears no relation to it. It is not dependent on hyperparathyroidism, and there is no change in the blood calcium and plasma phosphatase. It usually appears inadolescence, and after progressing for a number of years it may undergo spontaneous recovery. It is seldom that more than one bone is involved, but occasionally there may be lesions in two or three bones. Cyst formation is common; there may be multiple small cysts or one large cyst. Small giant-cell tumors may develop in the wall of the cyst. The pathological features are therefore very similar to those of generalized osteitis fibrosa. The lesion begins in the metaphysis, and spreads for some distance along the shaft. The epiphysis is rarely involved. The upper end of the femur, the humerus and the tibia are the bones most often involved. The first indication of the condition is often

the occurrence of a fracture. Not infrequently this has a beneficial effect, appearing to stimulate bone formation and lead to arrest of the disease. The exact nature of the condition is obscure, but it may be a perversion of the normal process of removal of calcified cartilage by vascular connective tissue preparatory to the formation of true bone.

Bone Cysts.—Cyst formation may occur as a complication in many diseases of bone. Bloodgood gives the following list in addition to osteitis fibrosa cystica: multiple chondromata, myxoma, giant-cell tumor, osteitis deformans, subperiosteal hematoma with a bony wall due to an ossifying

Fig. 489.—Osteitis fibrosa cystica of the femur complicated by sarcoma.

periostitis, and callus cysts. To these may be added bone abscess, echinococcus cysts, and osteomalacia.

PAGET'S DISEASE OF BONE

This rare and interesting condition, the exact nature of which is still unknown, was first described by Sir James Paget in 1876. It is also known as osteitis deformans, but as osteitis fibrosa is even more deforming, it will be seen that this term is misleading and undesirable. The essential feature of the disease is an associated softening and overgrowth of bone. Persistent bone pains form the chief subjective symptom in the earlier stages. It is usually regarded as a rarity, but Schmorl, examining the entire skeleton in his autopsies, collected 138 cases in the course of five years.

Clinical Features.—The bones principally affected are the skull, the vertebrae and sacrum, and the bones of the leg, but almost any bone in the body may be involved. As a rule the disease manifests itself in a number of bones, but in rare cases it may be confined to one bone; the diagnosis is then a matter of great difficulty.

The bones of the lower limbs are usually the first to be affected, but in a number of cases the disease may commence in the skull. The softened bones of the leg, having to bear the weight of the body, become bent; the femur bends outward, the tibia forward. The patient therefore becomes bow-legged. In addition to the bowing there may be a marked twisting, so that, as DaCosta remarks, the femur comes to look as though it had been grasped by the hands of a giant, bent in a bow, and then twisted. Other

Fig. 490.—Paget's disease of the skull showing the serrated appearance.

factors in addition to that of body weight must be responsible for the deformity, for the bones of the arm also become bent, although to a lesser degree. In this case the curve is backward.

Associated with the bending, or even before it occurs, there is a very characteristic thickening of the bone. The bone pains which are so constant a feature of the disease are felt particularly in the legs, seldom in the arms or head. They may be continuous or periodic. The bone pains may appear many months before any gross lesion can be detected.

Enlargement of the skull is almost always present at some stage of the disease. It may be the first sign to appear, and may first attract attention through the patient noticing that he has to buy hats of ever increasing size. The deformity in typical cases is so characteristic that it can be

recognized at a glance. The head becomes a triangle with the base above; the face usually escapes almost completely. The enlargement is due to enormous deposit of bone on the outside of the cranium; there is no endocranial thickening. To those cases in which the facial bones and the skull are thickened, whilst the other bones escape, the name *leontiasis ossea* is given.

The vertebral column is almost always involved, and a marked kyphosis develops in the dorsal and lower cervical regions. As a result of the kyphosis the patient shrinks in height, an occurrence which is aggravated by the bowing of the legs. There are cases in which a man has lost as much as a foot in stature.

The clavicles may be affected, and in exceptional cases the bones of the hands and feet. The pelvis may be broadened, the ribs thickened, and the chest deformed.

The X-rays show characteristic changes long before any deformity appears. There is great thickening and increase of density of the bone, and the vault of the skull presents a peculiar serrated appearance (Fig. 490). An X-ray picture should be made in all patients with chronic bone pains. There may be considerable difficulty in differentiating between the changes in Paget's disease and in bone syphilis. Wilhelm has drawn attention to the following points of distinction: in syphilis there is marked participation of the periosteum, whereas in Paget's disease there is none; the more or less advanced narrowing and obliteration of the marrow cavity in syphilis compared with the great widening of that cavity in Paget's disease; the sclerotic or finely porous quality of the newly formed bone in syphilis compared with a lengthwise splitting into lamellae often seen in Paget's disease.

The appearance and gait of the patient in the advanced stages is highly characteristic. The short squat figure with the bent shoulders, the curved back, the sunken chest, the long arms, and the great head hanging forward, waddles along with bowed legs, out-turned toes, and the aid of a stick, the living justification for the term osteitis deformans.

Fig. 491.—Tibia in Paget's disease.

The disease is slowly progressive, but may not shorten life, and is compatible with unimpaired mental activity.

Lesions.—In the early stages of the disease the bones are so soft that they can be cut with a knife. Later they may become extremely hard. As already indicated the essence of the disease is bone absorption associated with or followed by increased bone formation. There is a thick deposit of subperiosteal bone on the long bones and on the skull, and the surface is rough and irregular. The thick, hard, curved bones are very characteristic of Paget's disease (Fig. 491). The thickening is most strikingly seen on the cut surface of the skull cap, and a pathological diagnosis can readily be

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made from it alone (Fig. 492). *Microscopically* the lesions are of the same general type as in osteitis fibrosa. There is first a replacement of the
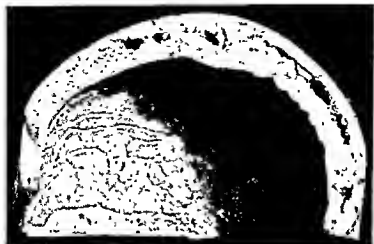
Fig 492.—Paget's disease of the skull Although the skull is so thick, it is also quite porous, and water runs through it with the greatest ease

original bone by connective tissue, and then a substitution of finely-porous cancellous bone which gradually becomes harder. Absorption and ossification go on together, but the latter outstrips the former so that the

Fig. 493.—Mosaic appearance in Paget's disease. × 215.
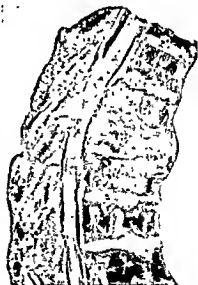
Fig. 494.—Osteogenic sarcoma in Paget's disease.

bone becomes thick though still finely porous. One of the most characteristic features of the microscopic picture is the great number and *irregular* arrangement of the lamellar systems, which is seen in no other dis-

ease of bone. This gives what is known as a *mosaic* structure (Fig. 493), due to variously shaped areas of new and old bone separated by ground substance. The porous nature of the bone can best be demonstrated by pouring water into the thick skull cap, when it will be found to escape as through a sieve. Cyst formation is very rare, and so is the formation of giant-cell tumors. The medullary cavity is filled with fibrous tissue. Paget's disease is a strong predisposing cause towards the development of osteo-genic sarcoma (Fig. 494). This has occurred in nearly 10 per cent of the recorded cases.

The *nature of the condition* is uncertain. At first sight it would appear that it was merely a variant of generalized osteitis fibrosa occurring at a later period of life with formative processes dominating the destructive ones. There is a very great increase in the plasma phosphatase, even more marked than that occurring in osteitis fibrosa. But the signs of hyper-parathyroidism which form so fundamental a feature of osteitis fibrosa are wanting. The blood calcium and phosphorus are normal, and there is no parathyroid hyperplasia. At the same time one is not prepared to say that there is no truth in the current idea that the two are variations of the same process. There is certainly nothing else satisfactory to put in its place, except the usual vague guess at hypothetical toxins causing a chronic inflammation of the bone.

OSTEOMALACIA

This disease is of extreme rarity on the North American continent, but is fairly common in the Rhine valley and in Northern Italy. It is a deficiency disease associated with malnutrition, and it was very prevalent in the Central Powers during and after the first world war.

The disease is one of middle life, and it is almost confined to women, especially those who are pregnant or who are exhausted through bearing large numbers of children. Many bones may be affected, but those exhibiting most of the effect of the disease are the lumbar vertebrae, the pelvis, and the bones of the legs.

All the symptoms are due to a decalcification of bone, the lime salts being removed, the organic part left uninjured, so that the bone can be bent, cut, and sometimes actually squeezed like a sponge. An excess of lime salts is excreted in the urine and the feces. The bone marrow is extremely vascular. The periosteum may occasionally lay down new bone on the surface, but there also calcification is very incomplete.

The vertebrae become compressed, *so that the patient may rapidly lose height*. Softening of the pelvis may lead to a deformity which may make normal delivery impossible. *The promontory of the sacrum comes forward, and the pressure of the heads of the femora drives the acetabula inwards*, so that the pelvic inlet is greatly distorted and narrowed. The thorax is compressed laterally. In the leg the bones are curved forwards and outwards. In its effects, therefore, as well as in its nature and causation the disease bears a distinct resemblance to rickets.

ACHONDROPLASIA

Another disease which bears some resemblance to rickets is achondroplasia, sometimes called fetal rickets. It affects bones developed in cartilage, that is to say the long bones and the base of the skull, whereas the bones of the face, developed in membrane, escape. The essential basis of the condition, as the name implies, is a malfunctioning of the epiphyseal cartilage, so that the long bones do not increase in length, and the result is a stunted dwarf with short arms and legs. The epiphyses are enlarged, and with the short *diaphysis* the *appearance of a long bone has been* likened to a collar stud. The head is large, the bridge of the nose depressed, the hands and feet squat, the fingers of equal strength—the so-called "trident hand."

The cells of the epiphyseal cartilage show no sign of proliferation, and although enlarged are not arranged in definite rows.

The cause of the condition is unknown, but may well be due to defective secretion on the part of one of the ductless glands which regulates skeletal growth.

MARBLE BONES

In marked contrast to osteomalacia this extremely rare condition, known also as *Albers-Schonberg* disease, is an osteopetrosis. It has a marked familial tendency. In place of the lamellae which characterize normal bone there are excessive deposits of calcium in osteoid tissue. The bones are brittle and easily fractured in spite of their density. It is a disease of childhood and youth. In the X-ray film the bone is dense like marble. All the bones are affected, and in addition the liver and spleen may be enlarged. The cranial and spinal foramina are narrowed, causing pressure on the nerves, and filling in of the marrow cavity replaces the marrow and results in marked anemia. The cause of the condition is unknown.

OSTEOGENESIS IMPERFECTA

This rare condition, also known as fragilitas ossium, is an affection of childhood in which the bones are imperfectly ossified. There is a marked hereditary and familial tendency. The child may be born dead with multiple fractures acquired in utero, it may be born alive and die afterwards from many fractures produced during delivery, or it may be born apparently healthy and only show evidence of brittleness during childhood and adolescence. There is a tendency for the condition gradually to disappear. A remarkable feature of the disease is that many of the patients have blue sclerotics: the color is due to partial visibility of the choroid through the sclerotic owing to some defect in that coat. Blue sclerotics may be associated with brittle bones in one member of the family, while the others have blue sclerotics but no special tendency to fractures. Otosclerosis may develop after the age of twenty years. The blood calcium and phosphorus are normal. The parathyroid glands may be enlarged. In one very severe case in a still-born baby which I examined the enlargement was very noticeable. In addition to the fractures there may be bony swellings, especially in the temporal region so that the ears are turned out and down, and sometimes in the frontal or occipital regions. The ossification of the skull may be so incomplete that it is a mere membranous bag or a few bony plates; if ossification has proceeded further the skull may present a large number of Wormian bones. The teeth are poorly calcified and may be translucent. The bones are very light and fragile. Microscopically the trabeculae are narrow and widely separated. Few osteoblasts can be seen, and it is possible that there may be a deficiency of phosphatase production.

FIBROUS DYSPLASIA OF BONE

This condition, which is readily mistaken for osteitis fibrosa cystica, was first described by Lichtenstein, and later by Lichtenstein and Jaffe. It appears to be an error in development, as a result of which fibrous thickenings of one or more bones are produced. These are often confined to one side of the body. In the severe forms, which are more likely to be seen in children, there may be pigmentation of the skin, premature sex development in females, premature skeletal growth, and hyperthyroidism. From this list it will be seen that the disease is obscure and little understood.

The lesions resemble in many respects those of osteitis fibrosa. The bone is expanded and the cortex thinned, the interior being filled with rubbery fibrous tissue. The new connective tissue is cellular in some places, with whorls of spindle cells, whilst in other places it is densely collagenous. New trabeculae of bone may be formed through metaplasia of the fibrous tissue. Small cysts, hemorrhage, and giant cells may be present. The disease is usually self-limited, and has no relation to parathyroid adenoma.

HEREDITARY DEFORMING CHONDRODYSPLASIA

The remarkable condition is known by a variety of other names, such as multiple cartilaginous exostoses, hereditary multiple exostoses, multiple

congenital osteochondromata, and diaphyseal aclasis. As the names imply, the disease is sometimes regarded as a form of neoplasm, sometimes as a hereditary disturbance of the metabolism of cartilage and bone.

Clinical Features.—The disease, which is about three times as common in males as in females, begins in early life. It is characterized by the appearance of multiple growths in the bones. These growths, however, are merely incidental, not the essence of the disease. They are as a rule first noticed during the first decade of life. Almost any bone in the body may be involved, but those affected are, in their order of frequency, the femur, tibia, humerus, fibula, radius, ulna, phalanges, ribs, scapula, and pelvic bones. It will be noticed that the flat bones as well as the long bones may be affected by the disease. The bones of the face and skull are rarely involved; they are laid down in membrane, not in cartilage.

The changes to be observed may be divided into two main groups: (1) growth retardation, and (2) proliferative changes.

Growth retardation may affect the form, length, and thickness of the bone. This may best be seen in the metacarpal bones. The different metacarpals may vary markedly in size and shape, and this is particularly true when X-ray pictures of the two hands are compared. Similar changes are seen in the scapulae and pelvic bones. The acromial process may be very large, the body and glenoid process very small. In most cases the bones attain to a normal length, but they remain thin and delicate. Such bones as the radius, ulna, tibia, and fibula may show a considerable amount of bowing, due probably to unequal growth of the two bones. Cyst formation may be visible in the X-ray picture. In a case of Carman's there were large cysts in most of the lesions, and the upper part of the shaft of the humerus was entirely cystic on both sides. The stature is stunted, owing to the short legs. The underdevelopment of the fibula may give rise to a condition of pes valgus, that of the radius may cause a marked deformity of the wrist.

Proliferative changes are to be observed both distal and proximal to the epiphyseal line. The early disappearance of that line itself is a striking feature of the X-ray picture. In the *epiphyses* there is enlargement and distortion of the bone. The neck and great trochanter (but not the head) of the femur, the condyles of the femur, and the head of the tibia may show great enlargement, but no definite outgrowths. In the head of the fibula and the acromial process of the scapula, on the other hand, distinct growths, epiphyseal in origin, may occur.

Changes in the ends of the diaphysis are well seen at the lower end of the femur and at both ends of the tibia. They consist of curiously shaped outgrowths, sometimes stalactite-like in form, which may encroach upon the epiphysis, but originate in the diaphysis.

In the shaft of the diaphysis the common change is the appearance of a number of definite exostoses or of nodular, partially organized swellings of the periosteum. The growths often appear as the result of an injury to the bone. It appears as if the bone were specially sensitive to injury, and reacts in this way. The nodules may gradually disappear, or may become completely ossified. The relation of the exostoses to the deformities due to retardation of growth is variable. In some forms of the disease the exostoses never develop. In other cases exostoses may appear in bones

which show no deformity, whilst some of the deformed bones may show none.

The disease ceases when skeletal development is complete. The patient usually comes to the surgeon about the age of puberty because of pes valgus, pressure symptoms, or general bone pains.

Pathology.—The nature of the disease appears to be a disturbance of bone metabolism occurring early in life, and it may be *in utero*. The metabolic studies of Honeij are worthy of note. This observer found that "in the stabilized stage of the disease calcium exchange differs little from that of a normal individual, whether the abnormal subject is maintained on a calcium poor or a calcium rich diet. In the progressive stage of the disease calcium metabolism is markedly different from the normal in that calcium is lost from the body." Nests of cartilaginous cells may be left under the periosteum covering the ends of the shaft. These remain uncalcified, but at a later date they may develop into cartilaginous exostoses or chondromas.

Ollier's Disease.—This rare condition is also called dyschondroplasia, but this term, which simply means a disturbance of growth of cartilage, is so similar to hereditary deforming chondrodysplasia, that it is undesirable unless distinguished by Ollier's name. It is a disease of the growing ends of bone in which normal ossification of cartilage fails to occur, so that areas of cartilage remain in the diaphysis. The disease may be limited to one bone, or nearly every bone in the body may be affected. The long bones are the common sites of the lesions. In the roentgenogram there are areas of rarefaction at the ends of the bones giving a striped appearance. As the child grows older this is replaced by a speckling due to dense calcification of the islands of cartilage. The abnormality is usually noted between the first and second years of life, when one limb is found to be shorter than its fellow. By about six years of age bending of the limbs may be apparent, a deformity due to weight-bearing or to the irregular rate of growth. The condition is not progressive after the period of growth is completed, but the deformities of course are permanent.

Morquio's Disease.—In 1929 Morquio described a familial form of generalized osseous dystrophy under the name of *chondro-osteodystrophy*. Although congenital, the symptoms are not usually observed for some time after birth. When the child assumes the upright position kyphosis is seen due to a wedge-shaped malformation of the bodies of one or more vertebræ at the thoracico-lumbar junction. There is none of the pain and spasm of Pott's disease. Other skeletal deformities develop, such as enlargement of the joints, knock-knee, depression of the sternum, and misshapen head. The neck is short and the head characteristically appears to sit in a concavity at the top of the thorax. In the roentgenogram there is fragmentation and distortion of the epiphyses of the long bones. The condition is essentially a dyschondroplasia, but in addition the cornea may be clouded and the skin thick and elastic.

OSTEOCHONDRITIS JUVENILIS

Within recent years a number of conditions have been described occurring in childhood and adolescence and affecting mainly the epiphyses. They are commonly known as osteochondritis juvenilis, but a better name would be non-suppurative epiphysitis. They are of importance clinically because they are easily mistaken for tuberculosis, especially in the hip and spine. These conditions have a number of features in common, and appear to be different manifestations of the same fundamental process in a variety of places. They have been described, largely on radiological appearances, by men whose names have been attached to the lesion, with the rather absurd result that a list of the varieties rather resembles the index of a dictionary

of medical biography. There is Perthes' disease, Köhler's disease, Osgood-Schlatter's disease, Kümmell's disease, Kienböck's disease, Sever's disease, and so on. They are much commoner in boys than girls, probably owing to the greater frequency of trauma in the male. The points in common are as follows: (1) They all occur in the young, usually between the ages of 5 and 15. The fact that a condition happens to occur in the epiphyses of a variety of bones, as well as the semilunar of the wrist, the tarsal scaphoid, and the anterior tubercle of the tibia, does not convert a single pathological process into a number of clinical diseases. (2) They affect epiphyses which have not yet fused and which are subject to special strain, either from trauma or owing to the attachment of some powerful muscle; the changes do not occur after the fusion of the epiphyses. (3) Symptoms are either slight or entirely absent. (4) The radiogram, on the other hand,
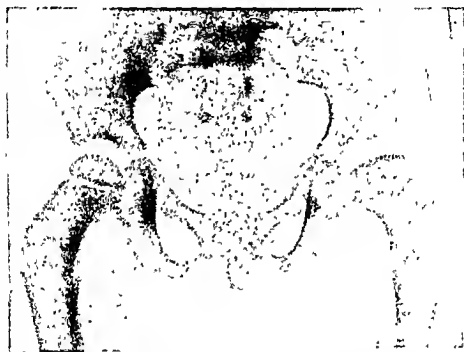
Fig. 495.—Perthes' disease: extreme flattening of the head of the femur.

shows marked changes, *i. e.*, flattening, fragmentation and increased density. When strain is relieved the symptoms gradually disappear, but the bony changes are permanent.

The *etiology* is uncertain. Trauma appears to play an important part, although it is always a difficult factor to assess. It is possible that the trauma may cause tearing of small vessels or at least interference with the blood supply, as a result of which a quiet necrosis of bone develops. A low-grade infection may be superadded, but of this there is no proof. It is quite possible that the essential process may be an aseptic necrosis. The restricted nature of the lesion may be accounted for by the fact that the center of ossification is everywhere surrounded by a wall of cartilage which resists the spread of the inflammatory process. The absence of nerves the center of ossification may account for the lack of pain.

Osteochondritis of the Hip (Perthes' Disease, Legg's Disease).—The condition commonly known as Perthes' disease is much commoner in boys than girls, usually between the ages of 5 and 10. A history of recent injury is often given. The earliest sign is a limp, usually accompanied by little or no discomfort, although occasionally there may be pain in the hip or knee.

There is slight restriction of mobility affecting movements of abduction and internal rotation. There is little or none of the atrophy of the buttock and thigh so characteristic of tuberculous disease of the hip, nor is there any thickening of the soft parts overlying the joint. A mild degree of irregular pyrexia is not infrequently present. The picture is that of a mild transient synovitis of the hip joint. After a varying period the symptoms disappear. Two signs, however, persist during life, thickening of the trochanter and limitation of the range of abduction.

The X-ray picture is absolutely characteristic, and it is by means of it that a final diagnosis is made. The head of the femur is distorted and flattened, and the neck is broadened and stunted (Fig. 495). The acetabulum becomes altered to conform with the final shape of the head. Where the discrepancy in size is great the acetabulum is shallow. A full discussion of these matters will be found in Platt's paper.

The *morbid anatomy* shows fragmentation of the bony nucleus of the epiphysis, which may be markedly disintegrated so as to resemble particles of mortar. As a result the head of the femur becomes flattened and splayed out, so that the end projects beyond the acetabulum. When healing occurs the fragments coalesce, and the bone regains some of its structure, but the flattening is permanent. Owing to the excellent response to conservative treatment there have been few opportunities to make direct observations, but Phemister has found the center of ossification of the epiphysis to be broken up into a number of small sequestra. Cultures and animal inoculation proved negative.

Fig. 496.—Köhler's disease. Marked atrophy of the scaphoid.

Osteochondritis of the Tarsal Scaphoid (Köhler's Disease).—The clinical features are similar to those observed in the hip, *i. e.*, slight pain on walking, a limp, and tenderness over the affected bone in a young child, followed later by clinical *cure*. The radiogram shows that the scaphoid is diminished in size, biconcave or flattened, and of increased density. Ossification of the scaphoid does not begin till the age of four, and the lesion takes the form of disintegration and necrosis of the center of ossification (Fig. 496).

Osteochondritis of the Tubercle of the Tibia (Osgood-Schlatter's Disease).—This occurs later, usually between the ages of twelve and sixteen. In a certain number of cases the tibial tuberosity does not develop from the epiphysis but from a separate center of ossification. As a result of direct trauma or of sudden strain through the ligamentum patellae, there is partial separation of the tuberosity, with the production of the usual symptoms of mild pain and tenderness. The radiogram as before shows fragmentation of the nucleus followed later by increased density.

Osteochondritis of the Os Calcis (Sever's Disease).—Here the lesion is in the posterior epiphysis of the os calcis, probably produced by strain on the bone acting through the tendo Achillis. Radiologically the epiphysis shows loss of normal architecture and increased density.

Osteochondritis of the Carpal Semilunar (Kienböck's Disease).—Although this condition is met with in adults, it appears to belong to the same group. There is a history of trauma to the hand, either a single severe injury or repeated minor ones. The radiogram shows narrowing of the bone and a patchy increase of the density.

Osteochondritis of the Spine.—Two rather different types of lesion may occur in the spine. (1) Vertebral epiphysitis affects the upper and lower epiphyses of the lower dorsal vertebrae. The usual time of onset is about the age of puberty. There is fragmentation of the epiphyses, the vertebrae become wedge-shaped, and kyphosis may develop. (2) Posttraumatic spondylitis (Kummell's disease) occurs as the result of injury to the back due to a fall from a height on the feet or buttocks or the impact of a heavy weight on the shoulders. After some months local symptoms develop, and theradiogram shows marked decalcification of a single vertebra with collapse of the body and the production of kyphosis.

Fig. 497.—Eosinophilic granuloma of bone. Many of the cells are eosinophils. × 500.

Osteochondritis Dissecans.—This is a non-infectious aseptic necrosis of a segment of subchondral bone, affecting principally the long bones of the extremities, and resulting in an osteocartilaginous sequestrum which may lie as a free body in the joint. The necrosis appears to be due to interference with the vascular supply. Trauma seems to be the chief etiological agent. The sequestrated fragment is covered by intact articular cartilage. The subchondral necrotic bone is separated from the normal bone by a bloodless fibrous tissue bed. The microscopic picture is one of necrosis with low-grade productive aseptic inflammation. Foreign body giant cells are present.

Eosinophilic Granuloma.—This rare condition is of importance because, while clinically and roentgenologically it closely resembles a malignant tumor of bone, it is benign and can be cured by operation or irradiation. The disease is characterized by the rapid appearance of a painful swelling in a bone, usually the skull, but sometimes a rib or a long bone, which may or may not be tender. The clinical condition has been mistaken

for osteomyelitis, tuberculosis, Ewing's tumor, and giant-cell tumor. There is a tendency to pathological fracture. It is a disease of childhood and early adult life, predominantly in males. There are no severe general symptoms, but there may be a considerable degree of eosinophilia. The gross lesion is soft, yellowish-grey, and expands the bone. *Microscopically* the lesion consists of large mononuclear cells with pale nuclei which can be classed as histiocytes, and large numbers of eosinophilic polymorphonuclears. The macrophages may contain ingested eosinophilic débris. If there has been destruction of fat there may be cholesterol crystals and giant-cell formation (Fig. 497). In view of the fact that not every case presents eosinophils, an alternative name is solitary granuloma of bone. Recent work suggests that the condition should not be regarded as a nosological entity, but that it is in reality a monosymptomatic form of Schüller-Christian's disease (skeletal lipoid granulomatosis) that often heals without becoming generalized (Green and Farber, Holm et al.).

RICKETS

Rickets is a constitutional disease making its appearance about the age of six months and continuing perhaps for several years. The active period of the disease is during the first two years, but its effects may accompany the patient during the remainder of his life. As the most striking features are connected with the osseous system the condition may be considered here.

Clinical Features.—The constitutional symptoms may be pronounced in the more severe cases. Anemia may be marked, and the sickly-looking, pot-bellied child is liable to acquire any infection that is going about. There is a general enlargement of the lymphoid tissue throughout the body, and the large spleen is one of the striking clinical features. Other signs that may be mentioned are the flabby condition of all of the muscles (which partly accounts for the pot belly), marked sweating, and delayed eruption of the teeth.

The interference with ossification, which is so important a feature of the pathology of the condition, is reflected in the very common bony deformities. It is these which persist long after all the active symptoms have disappeared, but in the course of time they also for the most part disappear. Owing to the defective ossification the long bones, especially those of the legs, may bend; the tibia bends forward, the femur outward. The epiphyses at the wrists, the knees, and the ankles are enlarged. A line of nodules is seen at the junction of the ribs and costal cartilages, the so-called rickety rosary. Curvature of the spine (either kyphosis or scoliosis), the "pigeon breast" due to a forward projection of the sternum, a vertical groove on either side of the thorax or a horizontal groove passing across the ensiform cartilage, are all of common occurrence. The pelvis shows various deformities, notably the flat pelvis; the sacral promontory may be carried forward and the acetabula inward, giving rise to the trefoil appearance seen in osteomalacia. This bony deformity may endanger the life of a woman at the time of childbirth long years after all active signs of the disease have disappeared.

The skull in rickets is characteristic. As the result of a heaping up of spongy bone at certain points bosses of bone are formed, particularly in the frontal and parietal regions. The effect is to make the skull square, and to give to the brow a lofty and intellectual appearance which is seldom warranted. A peculiar lesion may appear at the back of the skull where the head rests on the pillow, for here the bone may become eroded and thinned till it is of parchment-like consistence, a condition known as craniotabes.

What relation this lesion can have to the other bone changes in rickets it is difficult to understand.

The X-rays provide a valuable means of diagnosis and of estimating the effects of treatment. The change from the normal narrow line of the epiphyseal junction to the thick irregular line in rickets is very striking. This line may show definite defects of calcification. As the disease progresses decalcification takes place more rapidly at the center than at the periphery; the projecting ends of the compact bone retain their lime salts longer, so that the end of the bone may have a cupped appearance. The method is more valuable for indicating the progress of a case than for diagnosis, for, as Hess points out by the time that the X-rays demonstrate rachitic changes at the epiphyses, a well defined rosary is almost invariably present.

Morbid Anatomy.—The epiphyseal ends of the bone can be readily cut with a knife. At the points principally affected, viz., the wrist, knee, ankle, and the costo-chondral articulations the epiphyseal line presents a most remarkable difference from the normal. Instead of the thin,
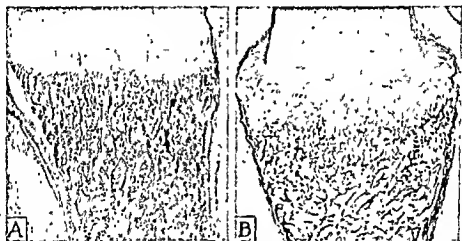
Fig. 498.—A, Thin normal epiphyseal line. × 8. B, Broad epiphyseal line in rickets; also nodule formation. × 8.

straight, regular line of ossification there is a wide, irregular band of grey material, which may be as much as 10 or 15 mm. in diameter (Fig. 498B), and in which can be seen white streaks of calcified tissue and bluish islands of cartilage. The shaft as well as the epiphyses may show a pathological condition in the shape of deposits of soft spongy bone both on the surface and in the medullary cavity.

Microscopic examination of the epiphyseal line shows that there is an abundant formation of new bone of a sort, but that this new bone is highly vascular and very imperfectly ossified. The cartilage cells are not arranged in regular rows as in normal developing bone, nor does the cartilage become calcified prior to the usual invasion by the marrow vessels. The result is that these vessels invade the cartilage in an irregular manner and to a great distance, leaving long tongues of cartilage projecting towards the medullary cavity. (Fig. 499.) These become converted into thick laminae of osteoid tissue, resembling bone morphologically, but lacking in the all-important lime salts. The bosses on the skull consist of similar

soft osteoid tissue. When the disease is checked lime salts are deposited in the osteoid tissue, which is thus converted into bone.

The periosteal disturbances are similar in character. The periosteum is extremely vascular, and deposits an abundance of new, spongy, poorly calcified bone, ill fitted to stand the strain of the weight of the body and the traction of the muscles. At the same time there is excessive absorption of bone in the marrow cavity, which still further aggravates the condition.

Etiology.—Rickets is a metabolic disorder, a deficiency disease, in which the inorganic constituents of bone, namely, calcium and phosphorus, are not built into the skeleton. Examination of the blood in rickets shows that either there is a low serum calcium with a rather low inorganic phosphate or normal calcium with a quite low inorganic phosphate. Of the two, the phosphorus appears to be the more important. Animals fed on a calcium-free diet develop osteoporosis but not rickets.

In 1921 Sherman and Pappenheimer demonstrated that rickets could be infallibly produced in rats by a diet adequate in calcium but deficient in phosphorus. Indeed so delicate is the reaction that by varying the amount of phosphorus in the food they could vary the degree of rickets produced. Webster and Leonard Hill have demonstrated that experimental rickets is accompanied by defective absorption of calcium and phosphorus from the intestinal tract. The administration of extra calcium, as Telfer has shown, merely decreases the absorption of phosphorus.

Rickets, therefore, can be produced experimentally in animals by feeding them on a diet poor in calcium and phosphorus. But there are two other factors of vital importance; these are the presence of a vitamin and of light. It was in 1919 that Mellanby presented to the Medical Research Council a report in which he showed that rickets could be produced in dogs by feeding them on a vitamin-free diet. This vitamin was contained in animal fats such as cream and butter, and it was present in relatively great quantity in cod-liver oil. At first it was thought that it was the fat-soluble vitamin A in the cod-liver oil which was the antirachitic substance, but we now know that vitamin A has no action in this direction, and that all the benefit is produced by vitamin D. In what exact manner the vitamin helps the body to utilize the calcium and phosphorus is not exactly known, but from the work of Webster and Leonard Hill it appears probable that it overcomes the defective absorption of calcium and phosphorus from the intestinal canal.

Rickets is much more common in the winter than in the summer months. It is much more common among the children dwelling in dark slums than among the children of the well-to-do. The difference lies in the action of light. The ultra-violet rays of sunlight, of the mercury vapor lamp, even of the carbon arc, will prevent rickets in an animal fed on a deficiency diet of such a character that it would certainly produce the disease. Rats fed on a rickets-producing diet are protected by being rayed for two minutes each day by the quartz-mercury vapor lamp. The rays, whether of sunlight or from a lamp, have no effect if passed through ordinary window glass, as the lead in it screens out the short length ultra-violet rays, but a number of substitutes for leaded glass are now on the market.

Pigmentation of the skin has an influence on the protecting effect of
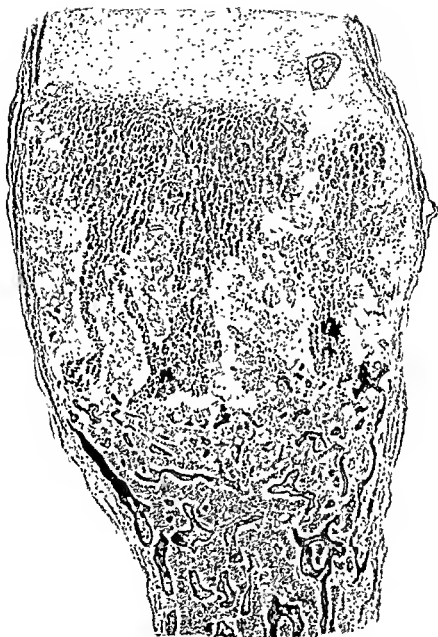
Fig. 499.—Rickets. Rib at site of line of ossification. The preparatory zone of cartilage is irregularly invaded by perichondral and marrow vessels. Calcification of cartilage lacking except in two or three foci. Invading blood vessels surrounded by osteoid tissue. Lamellæ of bone remain partly covered with osteoid tissue (MacCallum).

light. Thus white rats on a **deficiency diet** are protected by a certain exposure to light; for black rats under identical conditions the same exposure is without effect. This explains the **great prevalence of rickets among Negro** children.

Fig 500.—Infantile scurvy. Section of femur showing subperiosteal hemorrhage with periosteal bone formation. There are hemorrhages in the bone marrow and distortion of the line of ossification at the lower end. (MacCallum.)

The curative effect of light is intimately related to the action of vitamin D. This became evident when it was discovered that a direct action of the light on the child or animal was not necessary; the same effect could be obtained by radiating certain foodstuffs. These all contain cholesterol, the most remarkable result being obtained in the case of cod-liver oil. Apparently the light activates a parent substance and converts it into vitamin D. This substance is not cholesterol, but another sterol, ergosterol, which is invariably found in the presence of cholesterol. So potent is this action that 5 mg. of irradiated ergosterol has the same antirachitic effect as a liter of cod-liver oil. The curative action of light on the skin can be understood when we recall the large amount of cholesterol which the skin contains.

Rickets is a disease due to a faulty diet, especially when associated with lack of fresh air, lack of sunshine, and general unhygienic conditions, but the fault lies in the quality rather than the quantity of the food. A starved and emaciated child may show no sign of rickets, whereas a plump well-fed child may show marked evidence of the disease. The disease is confined to bottle-fed babies, except in the case of Negro children or when the maternal milk is insufficient owing to prolonged lactation. The exact fault in the diet has not been determined. A diet consisting almost exclusively of carbohydrates or proteins is almost certain to produce rickets. Bland-Sutton showed this in the case of the lions at the London Zoo. Rickets was so prevalent amongst the cubs, fed on lean meat, that not a litter could be reared for years. The addition of cod-liver oil and milk to the diet at once abolished the disease.

Scurvy-rickets.—Reference may be made in this place to Barlow's disease, which is usually regarded as a form of infantile scurvy developing in rickety children. It is very doubtful, however, whether the disease has any real relation to rickets. In contradistinction to rickets it is usually met with among the children of the well-to-do, children under 2 years of age who have been brought up on artificial and proprietary foods deficient in the necessary vitamins.

There is a marked tendency to hemorrhage from mucous membranes, the kidneys, etc., and under the periosteum at the ends of the long bones

(Fig. 500). As a result of the latter lesion the limb is painful, acutely tender, and is used so little as to arouse a suspicion of paralysis. The child screams whenever the limb is touched. Occasionally there is hemorrhage into the joint. The function of the epiphyseal cartilage is interfered with, whether or not on account of the hemorrhagic diathesis one cannot say; the bone ceases to grow in length, and separation of the epiphysis may occur.

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CHAPTER XXXI

DISEASES OF JOINTS

A joint is a structure of peculiar delicacy, and one which responds only too readily to injurious stimuli.

The structures which enter into the formation of a joint are the articular surfaces of bone covered by hyaline cartilage, the epiphysis, in some cases the epiphyseal cartilage and metaphysis, and the synovial membrane.

Anatomical and Physiological Considerations.—Our knowledge regarding the physiology of joints is still very limited, for a joint is a structure which does not attract the physiological investigator, but the recent experimental work of Timbrell Fisher has brought to light a number of new facts which will be referred to here.

Fisher draws a distinction between the central and the lateral areas of articular cartilage. The central articular area possesses no perichondrium, the surface being formed of clear matrix containing no cells. The lateral articular area is furnished with a delicate periochondrium continuous with the synovial membrane and containing well-marked capillaries. The nourishment of the articular surface is a matter of great importance, for articular cartilage is singularly devoid of blood vessels. There are three probable sources: (1) the capillaries in the subarticular cancellous spaces, which probably supply the deeper layers of cartilage cells; (2) the delicate offshoots to the lateral articular area from the circulus vasculosus, an arterial ring which encircles the joint at the deflection of the synovial membrane and gives off branches to the synovial membrane, the epiphysis, and the metaphysis; and (3) the synovial fluid, upon which alone the superficial layers of the central articular area are dependent. Fisher has shown that the protein content of the synovial fluid is less than half of that of the lymph, and this probably accounts for the feeble powers of resistance of this part of the articular cartilage, the readiness with which it degenerates, and the extreme slowness or absence of repair. He found that in persons between the ages of 60 and 70 over 90 per cent showed fibrillation of the central articular area. Experimental destructive lesions of the lateral part are followed by rapid and abundant formation of cartilage, whereas in the central part there is little or none. Moreover, after destruction of the central part there is a marked proliferation of the lateral part which appears to be compensatory in nature, so that the "lipping" which occurs in some forms of arthritis may be an attempt by the better nourished lateral portion to extend the articular surface.

The synovial membrane is lined in the parts most remote from the articular edges by a single layer of endothelial-like cells, but nearer the articular edges this layer is very deficient, so that it offers no obstruction to absorption from the joint cavity. At the margin and especially in the villi which occur chiefly in this region the membrane contains great numbers of cells filled with globules of mucin which can readily escape into the joint cavity

owing to the deficiency in the endothelial lining, an escape which is greatly facilitated by movements of the joint. So abundant are these mucinous cells in the synovial villi that they have been called "synovial glands." In chronic arthritis portions of the membrane may become detached and continue their secretion within the joint cavity.

Fisher's experimental work on loose bodies in joints has shown that when a piece of articular cartilage is detached, it almost always becomes attached to the synovial membrane, which lays down upon it layer after layer of cartilage. If such a body again becomes detached it may continue its growth, evidently deriving its nourishment from the synovial fluid, the nutritive value of which is probably increased by the inflammatory exudate.

Injection experiments show that absorption of diffusible dyes from the joint cavity occurs via the capillaries, but that colloidal solutions are absorbed by the lymphatics in the synovial membrane, thus agreeing with what we already know of the general principles of absorption. This absorption is greatly facilitated by passive movements of the joint or by allowing the animal to move about for a few hours. The material absorbed by the lymphatics can be demonstrated in abundance in the abdominal lymph nodes.

Fraser has shown that when carbon particles are injected into the circulation they tend to accumulate in the region of the circulus vasculosus, more particularly at the lower aspect of the neck of the femur, at the synovial refleetion on to the upper end of the tibia, and around the astragalus. A clump of tubercle bacilli may well imitate the behavior of the carbon partieles, and as a matter of fact these are some of the commonest sites of tuberculous disease of joints.

In the great majority of cases infection reaches a joint by the blood stream, although occasionally it may be introduced from without either by a wound or by an operation. A hematogenous infection may primarily attack the synovial membrane, or the attack may first fall upon the epiphysis or metaphysis, and later involve the joint itself.

The common diseases of joints are acute inflammation, tuberculosis, gonorrhea, and that peculiar and baffling group of chronic conditions which we designate by such terms as rheumatoid arthritis, osteo-arthritis, and arthritis deformans.

ACUTE ARTHRITIS

In considering the somewhat complex subject of acute inflammation of joints the difficulties that beset the way will be considerably smoothed by recalling some of the general principles of inflammation already discussed in Chapter II. Two of these principles may be restated here. In the first place the two most important causes of inflammation are trauma and bacterial infection. In the second place all forms of inflammation proceed to one of three terminations: (1) resolution; (2) suppuration with tissue death; and (3) repair with fibrosis. By applying these ideas to the particular constituents of any joint we have the pathology of acute arthritis in its varying forms.

Acute arthritis may arise in the following ways.

1. *Trauma.*—A blow, wrench, or sprain will set up an aseptic inflam-

mation confined to the synovial membrane, and usually transient in character. The presence of a loose body in a joint, or a displaced semilunar cartilage in the knee will act in a similar manner.

2. *A perforating wound* of a joint, by introducing infection from without, will give rise to acute inflammation.

3. *Spread of Infection from Neighboring Tissues.*—Inflammation of the adjacent articular end of the bone may involve the joint. That variety known as the acute arthritis of infants is worthy of special mention. Much more rare is spread of inflammation from the soft parts. Suppuration of a bursa or sloughing of the overlying tissues resulting from an injury affords examples of this mode of infection.

4. *Infection by the Blood Stream.*—Any condition in which organisms are circulating in the blood may be complicated by arthritis. The arthritis of pyemia forms a familiar feature in the general picture of that disease. Many of the acute infectious fevers may be complicated by arthritis. The organism of *acute rheumatic fever*, although it may attack many other tissues, has a special predilection for the joints. The gonococcus may set up an acute arthritis, although a slow proliferative type of inflammation is commoner. The pneumococcus may involve the joints as well as the lungs.

If the three possible modes of termination of inflammation be borne in mind it will not be necessary or desirable to discuss simple synovitis and septic arthritis in separate sections. The sequence of events depends entirely on the nature, intensity, and duration of the irritant. It is convenient, however, to distinguish between the mild and the severe forms of acute arthritis.

Mild Form.—A trauma, such as a sprain, or a mild non-virulent bacterial infection will give rise to a synovitis which, as a rule, will terminate in perfect resolution. The arthritis of acute articular rheumatism is somewhat similar in its pathology.

The *synovial membrane* becomes intensely red and congested, affording, should the joint be opened, a striking contrast to the pearly white color of the articular cartilage. An inflammatory exudate consisting mainly of serum with a varying number of leucocytes is poured into the membrane, which therefore becomes swollen, soft, and juicy. As a rule the fibrin-forming constituents do not appear in the exudate, which, on that account, is readily absorbed. Occasionally, however, these are present, and the more plastic and formative type of exudate is less likely to disappear leaving not a trace behind. The epithelial cells covering the surface are cast off and are found in varying numbers in the joint fluid.

The *synovial fluid* is increased in amount and altered in character. At first clear and translucent, it becomes somewhat cloudy, and is seen to contain floating flakes of fibrin. These may be deposited on the surface of the synovial membrane, so that the latter loses its normal shiny appearance. Desquamated epithelial cells and small numbers of leucocytes are present. The fluid is usually of a reddish tinge, owing to some of the distended vessels in the synovial membrane having given way. The extravasated blood does not clot, but becomes intimately mixed with the synovial fluid.

Under ordinary conditions all the elements of the inflammatory exudate

are absorbed, and resolution is complete. Should the joint not be kept sufficiently at rest the condition may become more or less chronic. The synovial membrane becomes permanently thickened and the joint is distended with serous fluid from which little absorption occurs. Melon-seed bodies derived from the original flakes of fibrin may be found in the joint.

Severe Form.—The ordinary bacterial infection of joints is of a more severe character than that indicated in the above description. Owing to thrombosis of the vessels suppuration with tissue death occurs, a condition of acute suppurative arthritis.

The *synovial membrana* is extremely congested, swollen, and so soft as to be almost gelatinous. It loses its epithelial covering and therefore its normal glistening appearance, fibrin is deposited on the raw surface, and the membrane, infiltrated with pus cells, becomes converted into granulation tissue.

The *synovial fluid*, greatly increased in amount, is at first opalescent due to the presence of flakes of fibrin, then milky from admixture with pus cells, and finally becomes frankly purulent. The infecting organisms are often found in the fluid, but not infrequently they are confined to the synovial membrane. Blood may be present owing to rupture of the inflamed vessels.

The cartilage soon loses its pearly-white appearance and becomes ulcerated, so that large areas of the underlying bone may be exposed and every movement is accompanied by excruciating pain. If the arthritis has been secondary to disease in the articular end of the bone the destruction of cartilage is particularly extensive, but even in the form which is primarily synovial there may be marked involvement of the bone. The ligaments become softened and give way, so that dislocation is common and the disintegration of the joint complete. The whole process is merely one of suppuration with tissue death, or in other words abscess formation.

In severe cases the periarticular tissues are frequently involved. The abscess may burst through the capsule of the joint and burrow between the surrounding muscles, sometimes to a considerable distance. It is well to bear in mind that when the capsule gives way and the pus passes into the periarticular tissue the acute symptoms may suddenly subside in a manner exactly analogous to a ruptured appendix. It is the tension, not the inflammation, which causes the pain, and when rupture occurs both the pain and the swelling may disappear.

It is a curious fact that in cases of pyemia where the joint is distended with pus, oily from breaking down of the subsynovial fat, hardly a sign of inflammation may be found after the joint has been opened and the contents washed away. There is some slight thickening of the synovial membrane, but the cartilage and bone are quite intact.

The result, provided that the patient escapes with his life, is that which invariably follows suppuration with tissue death, namely fibrosis with contraction. The opposing joint surfaces are bound together by adhesions with most serious results to the functional activity of the joint. The ankylosis is as a rule fibrous, but where the articular cartilage has been extensively destroyed there may be cartilaginous or even osseous union.

Acute Arthritis of Infants.—In young children, usually under 18 months of age, an acute epiphysitis is often associated with suppuration of the corresponding joint. The

infection begins in the rapidly growing part of the bone, either in the metaphysis or in the epiphysis itself. A small sequestrum is formed, and the pus perforates the articular cartilage and invades the joint. The perforation may be so small as to be quite overlooked, so that in acute arthritis in young children the articular end of the bone must be examined with great care and if necessary explored, even although no communication between it and the joint cavity can be detected.

Pneumococcal Arthritis.—This form of acute arthritis may occur under two sets of circumstances. It may occur as a complication of lobar pneumonia, and is most frequently seen in adults. Or, more particularly in young children, it may occur without any pulmonary involvement, being merely a manifestation of a general pneumococcal septicemia. In the first variety the arthritis appears just after the crisis of the pneumonia. As a rule only one and that usually a large joint is involved, the knee joint being the most commonly affected. The inflammation may advance to suppurage, and the joint is usually filled with pus which is of a greenish tinge, lacking in odor, and containing large numbers of pneumococci.

In the variety seen in children the patient is overwhelmed by a pneumococcal septicemia, but in some cases there is an absence of general signs of infection, and the bacteria are apparently carried from some focus such as the tonsil to the joint affected. Pneumococcal arthritis is always a serious complication, and a large number of the cases terminate fatally.

Scarlet Fever Arthritis.—This variety is of fairly common occurrence. In the later stages of the disease, especially in children with severe throat complications, there may be a general suppurative arthritis. At an earlier date, and more particularly in adults, a synovitis may occur chiefly affecting the hand and wrist and closely resembling articular rheumatism. The lesions are probably due to a streptococcal infection.

Typhoid Arthritis.—An occasional complication of typhoid fever is an arthritis which may remain serous or may go on to suppuration. It occurs late in the disease, and affects one of the large joints, most often the hip. In about half the cases backward dislocation of the hip occurs, owing to distension of the joint with pus and weakening of the ligaments. A polyarticular form is much rarer, and is more likely to be serous in type.

The typhoid bacillus may be found in the fluid, but in a considerable number of cases other pyogenic organisms are present.

Acute Rheumatic Arthritis.—Acute rheumatic fever is so purely a medical condition that discussion of it here would be out of place. Suffice it to say that, acute as may be the local joint condition, it never goes on to suppuration. Although in the main a synovitis, yet in severe cases there is considerable involvement of the subsynovial and periarticular tissues and ligaments. Whilst, therefore, the inflammation clears up completely in the joint affected at the moment in from a few days to a couple of weeks, yet in the more severe cases with periarticular change some degree of fibrosis with corresponding permanent stiffness must be expected.

Acute arthritis may occur as a complication in the course of many other infections such as diphtheria, measles, mumps, cerebrospinal meningitis, tonsillitis, etc., but fortunately only on rare occasions. The passage of a catheter or sound may be followed by an arthritis, due to the absorption into the blood stream of organisms from the urethra

TUBERCULOSIS OF JOINTS

Tuberculosis of a joint may be primary or secondary. It may be primary in the synovial membrane, or it may be secondary to a tuberculous focus in the articular end of the bone. In the young tuberculosis is usually secondary to a focus in the bone, whilst in adults the primary synovial form is much the commoner. The reason for this difference is that in children the growing ends of the bone are highly vascular and the scene of rapid cell proliferation, on account of which they are more vulnerable to attack. In the hip the secondary, in the knee the primary form is usually encountered.

When the spread is from the bone to the joint the primary focus may be situated in the epiphysis, but the metaphysis is more commonly involved. From the latter site the disease spreads to the circulus vasculosus

of the joint and thus reaches the synovial membrane. Occasionally, however, it may perforate the epiphyseal cartilage and invade first the epiphysis and later the joint cavity. The tuberculous pus may pour into the joint through a large opening in the articular cartilage, but usually that opening is quite small and may be no more than pinpoint in size.

Etiology.—The disease is most common in children, particularly before the age of six. Occurring more rarely in adult life, it is at the same time more unfavorable in type, and cases occurring above the age of 30 rarely do well. The adult cases are apt to be mistaken, at least in the early stages, for osteo-arthritis, as the principal features are limitation of movement, swelling of the joint, creaking on movement, and slight pain. Tuberculosis

Fig. 501.—Tuberculous arthritis.

of both bones and joints is by no means so uncommon in old age as is generally considered. Sir James Paget, indeed, mentions an example of the disease in a patient 91 years old. This is a point which needs to be emphasized, for many such cases pass undiagnosed because the possibility of tuberculosis has never been considered. The resisting power of these senile cases is very low.

The joints most commonly affected by tuberculosis are the hip and the knee, then the elbow, shoulder, and ankle. The wrist, often diseased in adults, is rarely involved in children. In children the hip is more often affected than all the other joints put together—provided tuberculosis of the spine be excepted.

In not a few cases the onset of the disease is preceded by a local injury, such as a blow or strain. The effect of such a trauma is to produce a local inflammatory exudate or effusion of blood, which provides an excellent soil in which the tubercle bacillus may settle. Diseases such as measles and influenza, which lower the general power of resistance, may act as predisposing agents.

Morbid Anatomy.—Although tuberculosis of a joint may commence either in the joint itself or in the adjacent bone, the end picture is similar in the two cases, so that a common description will suffice, the points of distinction being alluded to as they arise.

The *synovial membrane* is swollen, voluminous, and so redundant that it not only fills up all the pouches and hollows but occupies the greater part of the joint cavity. In color it is a dirty grey, but may appear cyanosed or plum-colored at operation owing to the action of the tourniquet The smooth shining appearance of the surface is lost, and a correct diagnosis can usually be made after a glance at the membrane. The surface may be studded with small tubercles, more particularly in the form secondary to bone disease. (Fig. 501.) Often, however, the tubercles are only seen when the membrane is incised. The consistence varies with the degree of connective tissue reaction, but the occurrence of a myxomatous or gelatinous degeneration frequently renders it soft and pulpy, although in the later stages it may be friable. The membrane eventually becomes converted into tuberculous granulation tissue, scattered throughout which are yellow areas of caseation.

The foregoing are the changes most commonly found, but two rare varieties may occasionally be encountered. There may b a great hypertrophy of the synovial fringes, similar to that seen in arthritis deformans. Or, in rare cases, large tuberculous masses may form, similar to the solitary tuberculomas which are sometimes found in the brain.

The *contents* of the joint vary. As a rule the cavity is filled with luxuriant masses of synovial membrane, and it is to this, combined with the periarticular changes to be described presently, rather than to distension with fluid that we must attribute the loss of the normal contour of the joint, the disappearance of the bony prominences, and the filling up of the natural hollows. The synovial fluid in such cases is little in excess of the normal, but it contains flakes of fibrin which may be deposited on the surface of the synovial membrane, imparting to that structure a shaggy appearance, or they may give rise to the formation of foreign bodies known as *melon-seed bodies* or *joint mice.*

In a small proportion of cases the joint is filled with a serous fluid, with comparatively little hypertrophy of the synovial membrane, a condition known as *tuberculous hydrops,* and comparable to that form of tuberculous peritonitis which is characterized by the presence of ascites. In other cases there may be a tuberculous empyema of the joint, the fluid which distends the joint being tuberculous and not true pus. The clinical signs of these two varieties may be remarkably similar, so that a correct diagnosis may not be made until an aspirating needle is introduced.

A peculiar and rare form of tuberculous arthritis is known as dry caries or *caries sicca.* It usually occurs in early adult life, and affects particularly the shoulder joint. As the name implies, there is a complete absence

of effusion and suppuration, the chief feature being a gradual wasting and absorption not only of the bone but also of the soft parts. There is marked stiffness and pain, but there is no interference with the general health, and the condition may progress to spontaneous recovery, although with permanent stiffness.

The *articular cartilage* becomes involved sooner or later, although, owing to the absence of blood vessels, the disease never begins primarily in the cartilage. The cartilage may be attacked from its superficial or from its deep surface. In the former, which is much the commoner, the diseased and superabundant synovial membrane begins to creep over the articular surface as ivy covers a wall. At first it can be readily separated (Fig. 502), but soon it becomes so adherent that it cannot be removed without tearing the surface. The cartilage loses its bluish tint and polished appearance, and becomes opaque and yellowish. Vessels penetrate from the granulating synovial membrane into the cartilage, producing a series of pits which gives the surface a rough and eroded appearance, so that in time the cartilage also becomes converted into granulation tissue and large areas of bone are laid bare. It is at this stage, when the bone has become exposed, that the "starting-pains" at night appear.

The tuberculous *synovial membrane* may become caseous, as in the more severe forms of infection. The destruction of the cartilage from the surface is then arrested. It may be continued, however, from the deep surface, by a zone of very vascular granulation tissue which attacks the cartilage from below. These subchondral granulations are quite different in structure from those of the synovial membrane; they contain no tubercles, epithelioid cells, or giant cells, and are composed of fibroblasts, numerous capillaries, and round cells. Phemister suggests that the subchondral granulation tissue is not tuberculous in nature, but is formed as a foreign body reaction to the dead cartilage. As these granulations do not contain tubercles they do not undergo necrosis and caseation, so that they may continue to absorb and detach the articular cartilage from below. The cartilage comes away in flakes, or in exceptional cases the whole surface may be exfoliated intact. I have seen a case of tuberculosis of the elbow in which, although when the joint was opened the articular surface showed no trace of ulceration, yet the entire cartilage covering the lower end of the humerus, the trochlear surface of the ulna, and the upper end of the radius could be stripped off as three separate sheets. Phemister has shown that pus contains enzymes capable of dissolving the ground substance of articular cartilage. As such pus is absent from a tuberculous joint, the detached cartilage may remain intact for a considerable period.

Fig. 502.—Tuberculosis of head of femur; the articular cartilage has been stripped off.

The bone now becomes the seat of a rarefying osteitis, although naturally in the form which is primary in the bone the osseous changes w"ll

already be well advanced. There is no new formation of subperiosteal bone, and the apparent thickening of the articular ends of the bone is entirely due to the changes in the ligaments and the soft parts of the periarticular tissues.

The *soft parts* may be extensively involved. The ligaments become soft and gelatinous and are finally destroyed, as a result of which there is great disorganization of the joint, so that "pathological dislocation" may occur. The muscles, tendon sheaths, and the overlying skin share in this gelatinous degeneration, the result of the tuberculosis toxins. This change is responsible for the appearance of the joint to which the name *white swelling* is sometimes applied. At a later date there may be definite caseation of the soft parts, with the formation of a cold abscess which may or may not communicate with the joint cavity. The fluid contents

Fig. 503.—Tuberculosis of hip joint. Extensive caseation of bone and destruction of articular surfaces.

of such an abscess are not true pus, but rather the product of breaking down caseous tissue, a curdy material mixed with blood serum. Should secondary infection occur, more especially if communication is established with the exterior, a true pyogenic or pus-forming infection will result.

Microscopic Appearance.—The synovial membrane presents the appearance of a granulation tissue in which tubercle follicles are scattered here and there. Giant cells are abundant, the tubercles present a reticulum of epithelioid cells, but caseation may be slight or absent. A tuberculous obliterating endarteritis followed later by a periarteritis is a very constant feature, and is no doubt responsible for the spread of the disease both in the synovial membrane and in the bone, leading as it does to lowering of the resistance of these tissues, whereby they become more vulnerable. Myxomatous degeneration of the ligaments and the fibrous tissue in the

periarticular soft parts is an important feature of the disease, being responsible, to some extent at least, for both the softening and the swelling which in many cases are so characteristic.

Terminations.—At any except the most advanced stage of the disease a natural cure may occur. The resulting condition of the joint will naturally depend upon the stage reached by the disease. If only the synovial membrane is affected the subsequent disability may be limited to a slight degree of stiffness. When, however, there has been extensive destruction of cartilage and bone, fibrous or even bony ankylosis may occur (Fig. 503).

Acute general tuberculosis is a not infrequent mode of termination in children, but it is remarkable how comparatively seldom phthisis is found in a child with a tuberculous joint.

Amyloid degeneration affecting the liver, spleen, kidneys, and intestine is an accompaniment of long-continued and profuse suppuration. No general rule can be given regarding the length of time that suppuration must be present before the amyloid change makes its appearance. It may come on in the course of a few months. Marsh and Watson mention the case of a laborer in whom, although there had been suppuration of the knee joint and the lower end of the femur for 20 years, no amyloid disease existed.

CHRONIC ARTHRITIS

When we come to the subject of chronic non-tuberculous arthritis we have to sail an uncharted sea, through thick fogs, and with few landmarks that are of any value. At the very outset we are confronted with the problem of nomenclature, a problem almost insurmountable, and certainly not yet solved at the present time. Everyone who writes on the subject appears to consider himself justified in employing a phraseology all his own. Two main groups may be recognized, rheumatoid arthritis and osteo-arthritis. Nichols, in his classic contribution to the morbid anatomy of chronic arthritis, uses the terms proliferative and degenerative arthritis. The proliferative group corresponds to rheumatoid arthritis, the degenerative group to osteo-arthritis.

RHEUMATOID ARTHRITIS

This condition, also well named *chronic infective arthritis*, usually occurs in women of between twenty and forty. It is not uncommon in children, where it is often associated with, amongst other constitutional symptoms, enlargement of the spleen and of the lymph nodes. Rarely it may commence in old age. It is one of the most important of the chronic disabling diseases, in Europe ranking first among all the diseases which cause disability and in America equalling tuberculosis in that respect. The economic loss which it entails is stupendous.

The attack first falls upon the small joints, especially the proximal interphalangeal and the metacarpophalangeal joints.

The wrist, shoulder, knee and temporo-maxillary joints may be affected. The hip usually escapes. The onset varies in suddenness. As a rule it is gradual and insidious, but occasionally it may begin with an acuteness suggestive of rheumatic fever.

Resolution may occur early, especially as the result of prompt treatment, or the disease may proceed on its progressive and inexorable course

to its terrible termination, leaving the patient twisted, gnarled, and crippled for life. The stiffness and deformity are due in part to ankylosis from adhesions between the articular surfaces, in part to contraction of the soft parts preceded by spasm of the muscles.

Swelling of the joint, a very constant symptom, is due to effusion into the joint, but also to a great extent to changes in the periarticular tissues, thus differing in an important particular from osteo-arthritis. The joint has a peculiar doughy feel, and there is no development of osteophytes at the margin of the bones. The skin over the joint may become stretched and glossy. In addition to the local manifestations of the disease there may be any of the constitutional disturbances described in the next section.

In a number of cases painless subcutaneous nodules may be found, more particularly on the extremities. They are a good deal commoner on the upper than the lower extremity. They are similar in character to the much better known subcutaneous nodules of acute rheumatic fever. The percentage of cases in which these nodules occur varies from 4 (Cecil) to 29.5 (Clawson).

Etiology.—The etiology of chronic infective arthritis is still very uncertain, but it seems probable that there are predisposing and exciting factors. Among the *predisposing factors* may be mentioned age, sex, heredity, exhaustion, and metabolic disorders. The first two have already been considered. The chief evidence for the last is the fact that the basal metabolic rate is below normal in 20 per cent of cases. The *exciting factor*, without which the others are harmless, appears to be chronic infection, probably streptococcal in character. The evidence for this is partly clinical, partly bacteriological, and partly pathological.

1. The *clinical evidence* consists of the following points. Many of the patients present unmistakable signs of chronic infection. They are pale, pasty and unhealthy looking; and they suffer from malaise, irregular attacks of pyrexia, palpitation and sweating. The removal of a focus of infection in the teeth, tonsils or elsewhere may be followed by a truly remarkable local change in the joint. Measures designed to combat infection may have a very beneficial effect on the disease. Over 15 per cent of cases give a previous history of rheumatic fever, which raises the important question as to whether rheumatoid arthritis should be regarded as a sequel to or as a chronic form of rheumatic fever.

2. The *bacteriological evidence* is the finding of bacteria in the joint. In the past, efforts to obtain direct evidence by culturing bacteria have been for the most part unsuccessful, but recent workers have obtained better results. Cecil and his associates obtained attenuated hemolytic streptococci from the joint fluid of 65 per cent of selected cases, and from blood cultures in 60 per cent. Cadham, working in Winnipeg, cultured the excised regional lymph nodes draining the affected joint and obtained a pleomorphic diphtheroid organism which appears to have both a bacillary and a coccoid stage in its life history. In all of these investigations it is necessary not only to use special media, but to keep the cultures for several weeks before pronouncing them sterile. The streptococci obtained from the blood and the joints are similar to those found in acute rheumatic fever, and the feeling is growing that acute rheumatic fever and

chronic infective arthritis are two manifestations of the same infective process.

3. The *pathological evidence* is the occurrence of inflammatory lesions in the synovial membrane of the joint and the histological appearance of the subcutaneous nodules. Clawson points out that these nodules have the same structure as the nodules in acute rheumatic fever and those produced by the subcutaneous or intradermal injection of streptococci. By culturing the nodules he has obtained streptococci in many cases. The nodules consist of collections of mononuclear cells similar to those found in the valvular and skin lesions of acute rheumatic fever, and may present small patches of necrosis. Timbrell Fisher points out that the so-called fibrinoid degeneration, so characteristic a feature of the lesion of rheu-

Fig. 504.—Chronic infective arthritis. Photomicrograph of the margin of the articular surface of a phalanx. Shows granulation tissue extending over the joint cartilage from ingrowth of the granulation tissue: 1, shows the joint cavity; 2, the articular cartilage; 3, the shaft of the phalanx. The joint cartilage is covered with a thick layer of granulation tissue, 4, which extends from the synovial membrane over the surface of the cartilage. (E. H. Nichols in Keen's Surgery.)

matic fever, is an important feature of rheumatoid arthritis. The dense connective tissue becomes rarefied so as to give an appearance like fibrin; with Masson's trichrome green stain the fibrinoid material is brilliant red whilst the normal collagen is vivid green. In some cases of rheumatic fever the arthritis may persist in a form indistinguishable from rheumatoid arthritis.

Morbid Anatomy.—The process at the commencement is essentially a synovial one, and it may never pass beyond that stage. Thus the disease might be called synovio-arthritis, just as the other main form is called osteo-arthritis. When the joint is opened there is seen to be a great proliferation of the synovial membrane which may form thick pulpy masses, or may present numerous fringes and tags. Marked effusion of synovial fluid contributes to the general swelling.

The synovial membrane may then begin to encroach upon the articular cartilage, forming a thick *pannus*, beneath which the cartilage becomes eroded and ulcerated (Fig. 506). The pannus (Fig. 504), covering the two articular surfaces fuses here and there to form adhesions, and in time the greater part or even the whole of the joint cavity may be obliterated (Fig. 505). The new tissue is usually fibrous, but occasionally it may be cartilaginous or even osseous, and the accompanying ankylosis will be of a corresponding character.

Fig. 505.—Chronic infective arthritis with ankylosis. Photograph of vertical section through phalangeal joint. Shows the distal phalanx, 1, dislocated forward and downward into the palm of the hand; the joint cavity, 2, is practically obliterated and replaced by loose, dense, fibrous adhesions. The joint cartilage has entirely disappeared; the trabeculae of the phalanges are less numerous and smaller than in normal bone. (E. H. Nichols in Keen's Surgery.)

The articular cartilage is not attacked only from its free surface. As a result of the action of the irritant the superficial portion of the epiphysis becomes converted into granulation tissue, and the process of erosion is continued upon the deep surface of the cartilage. The process is not entirely one of destruction, for osteoblasts may lay down new bone on both the superficial and deep aspects of the articular cartilage. It is in the spine that the bone formation is seen to best advantage, and bony ankylosis of the articular processes may convert it into a solid, rigid column.

One of the characteristics of the disease is the involvement of the periarticular soft parts, to which some of the general swelling is due. In time
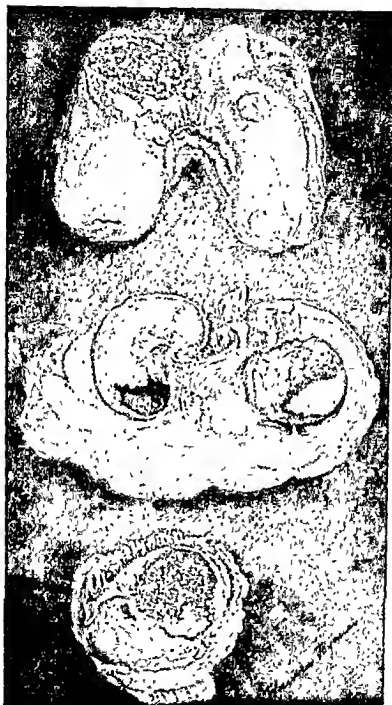
Fig. 506.—Rheumatoid arthritis. Ulcerative, ankylosing, and formative type in right knee joint. Upper figure is lower end of femur, middle is upper end of tibia, and lower is patella. Femur shows thinning of entire joint cartilage with one small, rounded, thickened mass on internal condyle. On external condyle is an irregular area which articulated with the patella, to which it was joined by bony ankylosis. The upper end of the tibia shows ulceration of the articular cartilage. The patella shows that the articular cartilage has been replaced by bony ankylosis with the femur. Along the upper margins are newly formed spicules of bone. (E. H. Nichols, in Keen's Surgery, vol. ii.)

the ligaments become softened and absorbed, a change which materially contributes to the deformities which form so distressing a feature of the end picture of the disease. Reference has already been made to the subcutaneous nodules. The muscles of the part undergo marked atrophy; the extensors of the fingers are particularly affected, so that the swollen fingers are characteristically flexed. Steiner and his associates have demonstrated that this atrophy is the result of a focal inflammatory process. These lesions, which involve widely separated muscles not necessarily connected with the joints, have therefore been called nodular polymyositis, are specific for rheumatoid arthritis, and are similar in nature to those found in the synovia and the subcutaneous nodules. Identical inflammatory lesions occur in the perineurium of the peripheral nerves (Freund et al.).

OSTEO-ARTHRITIS

Osteo-arthritis in its well-developed form is so sharply demarcated from chronic infective arthritis that to include the two under the same heading is quite unjustifiable. In many cases, however, the distinction is by no means so marked. This group corresponds to the degenerative arthritis of Nichols. It merits the name arthritis deformans quite as much as the preceding group, but as the most striking changes are those in the bones the term osteo-arthritis is an appropriate one.

The disease is one of middle and old age, being rarely seen in the young, and then only following trauma. It is commoner in females than in males. A notable exception to this statement is the hip joint, and here again the element of trauma in the etiology is probably of great importance, as that factor is to be looked for in men rather than in women.

The onset is slow and insidious, and is not accompanied by those symptoms of toxic absorption which have already been noted in chronic infective arthritis. Fewer joints are involved than in the infective variety, and quite often the disease may be confined to one of the large joints. When the hip alone is singled out the disease is called *Morbus coxae senilis*. The joints of the hands and feet are perhaps the most frequently affected, although the large joints, especially the hip, knee, and shoulder are often involved.

The appearance in the hand is highly characteristic. The knuckles are swollen into veritable knobs, and the distal phalanges are greatly enlarged, but the intervening proximal phalanges are often almost entirely spared. On the sides of the distal phalanges at the terminal phalangeal joints little bony outgrowths may appear. These are known as *Heberden's* nodes. Ulnar deviation of the hand is a characteristic deformity.

True ankylosis does not occur, as the pathology of the disease does not lend itself to such a complication, but there may be great limitation of movement owing to the formation of bony outgrowths around the joint. Occasionally, especially in the large joints, there may be undue looseness and mobility owing to absorption of the bone.

Etiology.—The nature and cause of osteo-arthritis are much more obscure than those of chronic infective arthritis. Its real nature is quite unknown. It appears to be a degenerative rather than an inflammatory process, so that the term arthritis may be somewhat misleading. The usual list—cold, exposure, disorders of metabolism—is given in the textbooks.

One cause really does appear to play an important role in a number of instances, and that is trauma, especially in the case of the hip joint following a fall on the trochanter. These cases pursue a more rapid course than usual.

There is no good evidence that the disease is due to bacterial infection. It has been suggested, and not without reason, that there may be a relationship between arteriosclerosis and osteo-arthritis. The disease usually occurs after middle age, and in many cases the arteries show marked endarteritis obliterans. It must be admitted, however, that arterial degeneration and advancing years go together; the stealthy hours, as Clifford Allbutt puts it, are constantly stealing away qualities of tissue and quantities of energy. Whether or not the articular surfaces share in these depredations we are really not in a position to say.

Keefer points out that the gross and microscopic changes in the knee joint associated with advancing years are identical with those of osteo-
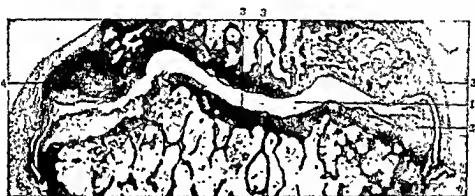
Fig. 507.—Osteo-arthritis. Photomicrograph of the phalangeal joint and adjacent phalanges. The line of the joint cavity is very irregular, 1, the cartilage has been almost entirely destroyed and shows only at the margins of the joint, 2, the articular surface of the phalanges where the cartilage has been destroyed is eburnated, 3, there has been a new growth of bone at the periphery of the joint (beginning Heberden's node), 4, the erosion of cartilage and eburnation, in this case, affects both sides of the joint articular facets. (E. H. Nichols in Keen's Surgery.)

arthritis. The patella showed lesions in 81 out of 100 consecutive autopsies. Erosions are common over the areas of contact subjected to most strain, weight-bearing, trauma, etc. There was no relation between the extent of the lesions and symptoms referable to the joints. Other observers have found similar lesions in other joints.

Morbid Anatomy.—The disease differs from chronic infective arthritis in that it commences in the articular cartilage with secondary involvement of the bone instead of primarily attacking the synovial membrane. At a later stage, it is true, both the synovial membrane and the periarticular tissues are implicated, but it is primarily a bone disease, a true osteo-arthritis.

The Cartilage.—Under the influence of the unknown causal agent the cartilage begins to degenerate. The smooth surface becomes roughened, being carried up here and there by delicate fibrils which give it the appearance of the pile of velvet.

The explanation of this appearance is seen in microscopic sections. The

ordinary arrangement of the cartilage cells becomes altered, and they form columns running at right angles to the surface, and separated by a matrix which degenerates and becomes converted into fine fibrillae running in the same direction. The cartilage cells enlarge, causing distension of their capsules, and the latter burst, discharging the cells into the joint cavity. The intervening fibrillar matrix gives the appearance of the delicate tufts already observed by the naked eye. The matrix in turn softens, and so becomes worn down by the movement of the opposing articular surfaces.

In course of time the entire thickness of the cartilage becomes eaten away, and the underlying bone is exposed. The process occurs irregularly, and as a groove forms on one articular surface a corresponding thickening, at first cartilaginous and later bony, is formed on the opposing surface. In this way a parallel series of ridges and furrows may be developed, such as are seen in no other disease. These are found in hinge joints such as the elbow and knee. They are naturally absent in joints with a ball and socket action. There are none of the fibrous adhesions between the articular surfaces which are so striking a feature in rheumatoid arthritis (Fig. 507).

The changes so far described occur in that portion of the cartilage which Timbrell Fisher calls the central articular area. In the lateral part of the articular surface the changes are quite different owing to the better nutritional arrangement and consequently the greater power of proliferation to which reference has already been made. In this area there is a marked proliferation of cartilage which, according to Fisher, always succeeds the degenerative changes in the central area, giving rise to a series of excrescences or ecchondroses, sometimes likened with justice to the drippings from a tallow candle. These may form a ring around the edge, producing an appearance of lipping. This new cartilage is largely formed by the synovial perichondrium. Many of these chondrophytes become ossified and converted into osteophytes, the surface of which ultimately degenerates and the subjacent bone becomes "eburnated." Fisher points out that the new formations actually extend the articular surface in many cases, and may be regarded to a certain extent as compensatory. The under surface of the osteophytes may be supported by buttresses which resemble those in the roof of a Gothic cathedral, and are required owing to the extremely open nature of the osteophytes which they support. Some of the processes may become detached and form foreign bodies in the joint.

The Bone.—The most characteristic changes are to be observed in the bone. As the cartilage is worn away the underlying bone is exposed. This bone becomes condensed, extremely hard, brilliantly polished, and comes to resemble ivory or porcelain, a process known as *eburnation*. This change is usually attributed to the attrition of the opposing articular surface, but it is difficult to accept this explanation as entirely sufficient, for it is seen in no other joint disease. The chronic irritant responsible for the disease may play a part equal in importance to that of the mechanical friction. It is difficult to explain otherwise the occasional occurrence of this change in such bones as those of the carpus, where the process of attrition is at a minimum. The polished surface is sometimes pitted as if wormeaten. This is due to exposure of the Haversian canals of the underlying bone. The remarkable series of ridges and furrows already described may break the smooth surface of the bone.

The bone deep to the condensed layer undergoes a slow process of rare-faction and absorption. This is well seen in the hip joint, where the greater part of the head and neck of the femur may become absorbed. Irregular new bone formation may go on at the same time at the margin, so that the atrophied head of the femur is surrounded by excrescences which give it a mushroom-like appearance (Fig. 508). The acetabulum undergoes similar changes so that it becomes enlarged in an upward and backward direction, and surrounded by osteophytes. The presence of these periarticular processes greatly interferes with the action of the joint.

Fig. 508.—Osteo-arthritis. Extreme erosion of the head of the femur, with polishing and exostosis formation. (MacCallum.)

The Synovial Membrane.—Although the disease process is not primary in the synovial membrane, sooner or later that structure undergoes characteristic changes. It becomes thickened, shaggy, and a series of fringes and tags hang from the surface of the capsule into the interior of the joint. In many of these tags cartilaginous change occurs, and they may become detached, giving rise to "joint mice."

The *synovial fluid* may be increased to a moderate extent in the early stages of the disease, and is usually somewhat milky owing to the discharge into it of the cartilage cells. Later the effusion becomes absorbed.

The Ligaments.—The gradual process of dissolution which has already been described as occurring in the cartilage and bone involves the ligament also. There is no violent destruction, but the ligaments simply melt away as if under the action of some solvent, causing great disorganization of the joint, with, in some cases, spontaneous dislocation. The lateral ligaments of the knee and even the cruciate ligaments may entirely disappear.

Neighboring tendons may share a similar fate. The best examples are seen in the shoulder joint where the intra-articular portion of the long tendon of the biceps and the tendons of the scapular muscles attached to the tuberosities of the humerus may become destroyed.

The Periarticular Tissues.—These often show changes which it is difficult to explain, and which would rather be expected in chronic infective arthritis. Wasting of the surrounding muscles is often extreme, and suggests an additional factor besides disuse. An edema of the subcutaneous tissues may extend for some distance beyond the joint, and the overlying skin is pale, tight, and shiny. When the edema passes off the skin is thin and wrinkled like crinkled tissue paper.

Reference has already been made to *Heberden's nodes.* These bony nodules originate as soft cystic lesions on the terminal joints of the fingers. They are lined by a smooth membrane and contain a small quantity of clear gelatinous material. The early soft lesions were recognized by Garro in 1876, and were redescribed by Nachlas in 1932. I have seen similar lesions in a patient who showed no evidence of arthritis two years after removal.

A COMPARISON BETWEEN THE TWO FORMS OF CHRONIC ARTHRITIS

Chronic Infective Arthritis	*Osteo-arthritis*
A disease of early adult life.	A disease of over middle age.
Symptoms of constitutional disease, suggesting infection.	None.
Synovial membrane and periarticular tissues chiefly affected.	Cartilage and bone chiefly affected.
May be acute in onset and run a rapid course.	Essentially chronic.
Hip joint rarely affected.	Hip joint often affected.
Effusion into the joint common.	Effusion into the joint rare.
Fibrous adhesions between articular surfaces.	Any rigidity due to bony outgrowths around joint.
No Heberden's nodes.	Heberden's nodes may be present.
Many joints involved, usually in a symmetrical manner.	Often only one joint affected; usually symmetrical when multiple.
No relation to previous injury or disease of joint.	Previous injury or disease frequent.

SPONDYLITIS DEFORMANS

In many cases of osteo-arthritis the small joints of the spine are also involved. The vertebrae are locked together by bony outgrowths and there is a tendency to bony hypertrophy. This naturally causes a certain amount of rigidity of the back.

Quite unrelated to ordinary osteo-arthritis is the remarkable and rare condition known as *Marie-Strümpell spondylitis* or spondylitis deformans. Indeed it is perhaps more nearly related to rheumatoid arthritis. The etiology is unknown; indeed little has been added to our knowledge of the condition since the classical paper of Pierre Marie in 1898. Marie himself named it *spondylose rhizomelique* because in his cases, in addition to the spinal lesions, there was more or less complete fusion of the hip and shoulder joint, *i. e.,* the joints at the roots of the limbs. The derivation from the Greek is *spondylos* meaning vertebra, *rhiza* meaning root, and *melos* meaning limb. The small joints are not involved. The disease is commoner in men.

In true spondylitis deformans the cardinal factor to be found is rigidity. The spinal column is sometimes so stiff and straight that it suggests the

term "poker back." Later in the disease the normal spinal curvatures may be lost, and the column is converted into a bow with its convexity backwards. The miserable patient becomes more and more bowed down, till ultimately the chin may rest upon the sternum and he is unable to look up. Ankylosis of the costovertebral joints results in such a fixation of the thorax with corresponding interference with respiration that any respiratory disease is apt to prove fatal.

So-called neuralgic pains (although there is no narrowing of the intervertebral foramina to account for pressure symptoms) are of frequent occurrence. These are principally felt around the thorax owing to pressure on the thoracic nerves, and down the back of the thigh from pressure on the great sciatic nerve. The corresponding muscles may be markedly atrophic.

Morbid Anatomy.—At autopsy there is extensive and complete ossification of the articular ligaments and intervertebral discs. There is ankylosis, complete and bony. The disease begins in the intervertebral cartilaginous discs, which gradually melt away. Osteophytic formation and lipping of the articular margins interfere with movement. It is, however, when the bodies of the vertebrae become fused together into one rigid mass that the real trouble begins. Moreover the ligaments share in the process. The anterior common ligaments may become converted into a rod of bone which binds many vertebrae firmly together. The ligamenta subflava and the interspinous ligaments may also become ossified. There is at present no evidence as to the nature of the primary lesion of fibrous structures which is responsible for the ossification. Swaim suggests that for some years the rigidity is due to muscle spasm the object of which is to protect against the pain caused by movement, and that the later ossification represents nature's method of permanent immobilization of the spine to prevent strain and motion and inflammation in the ligaments. This idea forms the basis of treatment by early immobilization so that ossification may be forestalled.

SPONDYLOLISTHESIS

This condition, which etymologically means the slipping of a vertebra, is a gradual forward displacement of the fifth lumbar vertebra (together with the superimposed vertebral column) over the first segment of the sacrum. It has long attracted the attention of the obstetrician on account of the consequent narrowing of the antero-posterior diameter of the pelvic inlet, and more recently it has been suspected as a cause of low back pain and even of sciatica. The use of the X-rays has shown the lesion to be a comparatively common one. It may be met with at almost any age.

The essential defect responsible for the displacement is a separation of the neural arch on each side between the superior and inferior articular processes. For long it has been believed that this separation was due to failure of fusion of two centers of ossification on each side of the neural arch (Neugebauer), but, as Batts remarks, this is a conjecture, not a proved fact. Trauma undoubtedly plays a part in many cases; the trauma may be sudden or may be repeated. It may tear away the fibrous attachment between the neural arch and the body of the vertebra. Lordosis may play a part, because in marked lordosis the sacrum is nearly hori-

zontal, and thus forward slipping of the fifth lumbar vertebra is facilitated. Hitchcock has shown experimentally on still-born children that hyperflexion of the spine, often with little force, readily causes fracture of the neural arch in the lower lumbar region, and he suggests that trauma during delivery may be responsible for the initial lesion.

Whatever may be the exact etiology, there is a telescoping of the spine into the pelvis, with marked narrowing of the pelvic inlet. The trunk appears to be shortened, and a characteristic skin furrow runs transversely round the trunk in the region of the loins. The space between the costal margin and the iliac crests is diminished.

CHARCOT'S DISEASE OF JOINTS

It was in 1868 that Charcot first described the peculiar disorganization of joints which may occur in the course of locomotor ataxia. Since that time little has been added to our knowledge of its essential nature. It is usually regarded as being due to interference with the trophic nerve supply to the joint, but this seems by no means a satisfactory explanation. Why should the disease in some cases appear with such dramatic suddenness, and why should the condition be usually confined to only one joint? A trophic neurosis hardly seems to account for such phenomena. It has also been suggested by Strümpell that it is a purely syphilitic lesion. The pathology of syphilis, however, presents no analogy to this condition. Moreover, identical lesions are found in the arthropathy of syringomyelia, which is certainly not a syphilitic disease. Charcot's disease must, therefore, be still regarded as an unsolved problem.

The joint affection may occur at any stage of tabes. Not infrequently it is quite an early symptom, and occasionally it may be the first indication of the disease. I have seen a patient with well advanced Charcot disease of the ankle and commencing disease of the elbow in whom there was not a single sign of tabes. Both the blood and the spinal fluid gave a four plus Wassermann reaction. In about 80 per cent of cases the joint involved is in the lower limb, owing to the site of the cord lesion being usually in the lumbar region. The knee, the hip, and the ankle are the principal sufferers, but the joints of the foot or of the upper limb may be attacked. As a rule only one joint is involved.

The onset is usually slow, and the condition is mistaken for osteoarthritis, with which it has many features in common. There is gradual enlargement of the joint, due in part to swelling of the soft tissues, accompanied by increasing weakness and disability, until finally the joint is completely disorganized and flail-like, and can be moved freely in all directions. Complete absence of pain is the most characteristic and remarkable symptom, and to be able to move about a profoundly diseased knee joint in all directions without any discomfort to the patient is apt to be somewhat startling to the examiner.

Not infrequently the onset is much more rapid, and the joint becomes painlessly distended with fluid within a couple of days. Destructive processes proceed with great rapidity, and the ends of the bones melt away like snow before the sun.

Morbid Anatomy.—The joint changes vary with the acuteness of the

course. In the more chronic forms there is, at least at first, a distinct resemblance to osteo-arthritis. There are the same wearing away of the cartilage, exposure and destruction of the bone, and thickening of the synovial membrane which is provided with numerous fringes and tufts.

Fig. 509.—Charcot's disease of the ankle joint. Natural position of the foot without the joint being forcibly opened. The extraordinary destruction of bone is very evident.

In some cases there may even be new formation of bone, as evidenced by the presence of osteophytes and lipping of the articular surface.

In the acute cases and in the later stages of the chronic cases the process of dissolution and disintegration reigns supreme. In the case figured in the text (Fig. 509) the interior of the ankle joint presented an extraordinary appearance of disintegration, as if some powerful solvent had been

poured into it which had eaten away all the solid structures. A great yawning cavity filled with chocolate-colored fluid contained a number of fragments of bone, including the external malleolus. Into this cavity projected a ragged stump representing the lower end of the tibia. The greater part of the astragalus had vanished, the only portion which was capable of any function being the head. Nowhere was there any evidence of new bone formation. Nothing further from the picture characteristic of osteo-arthritis could be imagined.

Arthropathy in Syringomyelia.—An arthropathy which might well be called Charcot's disease occurs in syringomyelia. As the gliosis of this nervous disease involves the upper segments of the cord, the joints affected in about 80 per cent of cases are those of the upper limb. The anatomical changes are the same as those of tabetic arthropathy, but suppuration is liable to occur owing to infection from the burns and trophic sores which are so commonly present on the hands.

HEMOPHILIC JOINT

In hemophilia, in addition to hemorrhages from the skin and mucous membranes, there may be hemorrhage into one of the large joints. Such hemorrhage may be the result of an injury or it may be spontaneous. The joints most frequently affected are the knee, elbow, and ankle. If this hemorrhage is repeated at intervals the joint becomes swollen and stiff.

Morbid Anatomy.—The appearance when the joint is opened will naturally depend upon the amount of time which has elapsed since the last hemorrhage. It may contain old or recent clot. Apart from this, however, an interesting change will be observed in many cases in the articular elements, a change which closely resembles that seen in osteo-arthritis. The cartilage is fibrillated and eroded, the underlying bone is exposed, the articular edge is surrounded by osteophytes, and the blood-stained synovial membrane is thickened and presents numerous villi.

The resemblance of the joint lesions in hemophilia to those of osteo-arthritis are of great interest. If the presence of a chronic irritant in a joint in the former disease can induce such a series of changes, it encourages a search in the latter for some similar etiological factor.

Pulmonary Hypertrophic Osteo-arthropathy.—This peculiar condition, affecting both the bones and joints, was first described by Marie in 1890. It occurs as a complication of chronic pulmonary disease, notably tuberculosis, bronchiectasis, and empyema. A somewhat similar clubbing of the fingers is met with in chronic heart disease, especially of the congenital variety with marked cyanosis. Indeed it appears probable that the two conditions are really identical, simple clubbing of the fingers being merely an early stage of hypertrophic osteo arthropathy.

In a well-developed case there are two principal changes: (1) a bulbous swelling of the fingers and toes—the well-known "clubbing" (Fig. 510), (2) periosteal hypertrophy with subperiosteal deposits of new bone. The clubbing is confined to the soft parts, and is apparently due to hyperemia of the blood vessels and an accompanying fibrous thickening of the subcutaneous tissues There is marked thickening and curving of the finger-nails—the "parrot beak" deformity. There is no corresponding change in the terminal phalanges.

The bony changes are probably due to a combination of hyperemia from the restricted pulmonary circulation and a toxemia from the primary lesion. The changes commence in the hands and feet, but later all the long bones may show the typical subperiosteal deposits. In an interesting case described by Paterson in which the bony changes were associated with the presence of a mediastinal tumor, the deposits of new bone largely disappeared as the result of deep X-ray therapy to the tumor which also showed a marked decrease in size.

Two factors appear to play a part in the etiology. (1) The absorption of toxins from a septic focus in the lung or pleural cavity is undoubtedly the most important cause of

the chronic periostitis. (2) Insufficient aeration of the blood seems to be capable of bringing about somewhat similar changes, for this is the only factor apparent in the cardiac case, although in these cases congestion must also be taken into account.
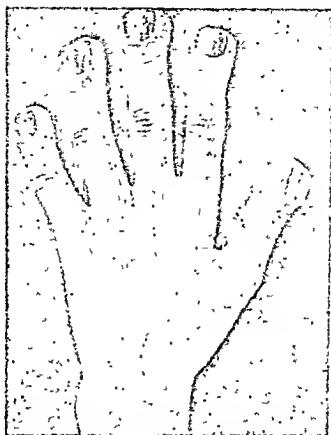
Fig. 510.—Extreme clubbing of fingers with broadening of distal extremities and deformity of finger-nails in Dr. Howard's case of pulmonary stenosis with ventricular septal defect, male aged 23 years. (Abbott, Blumer, Bedside Diagnosis.) (From a painting by Miss Hortense Douglas, Montreal General Hospital.)

GONORRHEAL ARTHRITIS

One of the common and important causes of arthritis is gonorrhea. The joint involvement is most frequent at the end of the third week or during the period of decline, but it may occur many months after the acute attack when only a slight gleet remains to tell the tale.

The gonorrhea need not be urethral in type. A gonorrheal conjunctivitis or vulvo-vaginitis may be followed by arthritis. It is well to note also that not all cases of arthritis associated with a urethral discharge are gonorrheal in nature, as organisms other than the gonococcus may reach the joints from the urethra.

The process is a metastatic one, and the organism reaches the joint by the blood stream. Owing to technical difficulties it is often impossible to isolate the gonococcus from the exudate in the joint. In long-standing cases this may be due to the organism having died out.

Although gonorrheal arthritis is a common disease, the percentage of

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thickness, and to an even greater extent in the subsynovial connective tissue and in the periarticular soft parts. The result is that, even although effusion is as a rule very moderate in amount, there is a marked chronic swelling of the joint which so closely resembles that of tuberculosis that the French have given the name of "syphilitic white swelling" to the condition. If such a joint be opened it will be found that the irregular and nodular thickening of the membrane is very different from the tubercle-studded surface so often seen in tuberculosis. In addition to the synovial involvement there may be, as is but natural, gummatous erosion of the bone and cartilage, so that the condition is sometimes known as syphilitic osteo-chondro-arthritis. The disease is not particularly common, for Fournier only found 30 cases in 5000 syphilitics.

In the *osseous form* the disease begins in the articular ends of the bones, which become enlarged, and spreads later to the synovial membrane. Nocturnal bone pains are therefore a prominent symptom.

It will thus be seen that there are three principal forms of joint disease in acquired syphilis: (1) the simple synovitis of the secondary stage, (2) gummatous synovitis, and (3) gummatous osteitis.

Congenital Syphilis.—We may distinguish two main forms of joint disease in congenital syphilis.

1. *Clutton's Joints.*—This is the name applied to a symmetrical serous synovitis described by Clutton in 1886 as associated with congenital syphilis. Both knee joints may be filled with fluid, but the patient experiences hardly any pain or even discomfort. Other joints may become involved in the course of several months. The usual age incidence is from 8 to 15. It is much commoner than deafness in Hutchinson's triad. Synovial fringes may fill the joint cavity with soft gelatinous material, and the thick synovial membrane may be infiltrated with inflammatory cells and studded with gummata. In other cases there may be true hydrops with very little synovial change.

2. *Syphilitic Epiphysitis of Infants.*—The neighboring joints may be involved in this form of bone disease. The epiphysis is enlarged, the joint swollen, and there may be tenderness and pain. Owing to the frequent separation of the epiphysis the condition is sometimes called syphilitic pseudoparalysis.

Other rare forms of joint disease in congenital syphilis have been described by Fournier, Bowlby, and others.

LOOSE BODIES IN JOINTS

Loose bodies in joints are of common occurrence, but there is still great diversity of opinion as to their nature and origin. The variety of the structures which may form these bodies adds to the difficulty of the subject.

The loose bodies may be divided into two great groups: (1) fibrinous loose bodies; (2) loose bodies composed of organized connective tissue. The latter may be fibrous, fatty, or cartilaginous. All varieties of loose bodies are commoner in diseased joints, especially in tuberculosis, osteo-arthritis, and Charcot's disease. What may be called the classical loose body, that composed of cartilage, is found in joints which are otherwise

healthy. All of the bodies are most common in the knee and elbow, although they also occur in other joints.

Fibrinous Loose Bodies.—In many joints the seat of tuberculosis or osteo-arthritis there may be found peculiar, small, rounded, or elongated bodies resembling melon-seeds or rice-grains (Fig. 511). They are usually numerous, sometimes indeed there may be hundreds present, but occasionally there is only one, in which case it may attain a considerable size. They are of moderate firmness, and often present a laminated structure similar to that of a grain of rice. Microscopically they display a vaguely fibrillar structure.

They are probably formed by a fibrinous change in the surface of the synovial membrane, but the exact mechanism is by no means clear. Once formed they may increase in size owing to deposition of fibrin from the fluid exudate which is always present. They are also found in abundance in synovial sheaths and bursae the seat of tuberculosis. The greatest number I have ever seen was in a case of tuberculous compound ganglion of the wrist in which the large synovial-lined cavity was simply packed with melon-seed bodies.

These fibrinous bodies impart a characteristic crackling sensation to the palpating finger. They do not give rise to the well-known symptoms due to impaction of a loose body in a joint.

Masses of fibrin may arise from blood effused into a joint. These, of course, are quite distinct from the melon-seed bodies.

Fibrous and Fatty Loose Bodies.—Under a variety of circumstances tags of fibrous tissue or fat may be formed, which tend to become more and more pedunculated, till finally they separate and form loose bodies.

Fig. 511.—Melon-seed bodies in tuberculous synovitis.

As the result of an injury the synovial membrane may be torn, and the constant irritation induced by the movements of the joint sets up a condition of chronic inflammation, as the result of which a thickened and finally pedunculated tag is formed.

A much more important cause is the presence of tuberculosis or osteoarthritis in the joint. In both of these diseases the synovial membrane may present a fringed and villous appearance, and one or more of these fringes may give rise to loose bodies. In a given joint some of the bodies may be free, some still attached by slender pedicles, and yet others may appear as if they never could become free.

Arborescent lipoma is the name given to the exuberant fringing of the synovial membrane sometimes seen in chronic arthritis. It is very

prone to give rise to the formation of loose bodies, and is of course in no sense a true lipoma.

Cartilaginous Loose Bodies.—This is the most interesting and important group of loose bodies, and it is these which give rise to the classical symptoms of loose body in a joint. They may be divided into three groups: (1) osteophytes; (2) traumatic fragments in otherwise normal joints; (3) synovial chondromata. The osteophytes, it is true, owe their existence as separate loose bodies to trauma, but the special significance of trauma in the causation of the second group will become apparent when that group is considered.

1. *Osteophytic Loose Bodies.*—An osteo-arthritic joint frequently presents osteophytic outgrowths so prominent and pedunculated that it is little wonder that they become detached as the result of even a trifling injury. The chondro-osteophyte may be completely separated, or may remain attached to the joint margin by a slender pedicle.

When such a fragment is examined closely it will be found that the bone at the site of fracture is completely dead, and that the periphery consists of well-developed fibro-cartilage with comparatively few cells. It is seldom that more than two or three of such bodies are found in a joint, and often there is only one. There may be in addition several cartilaginous loose bodies derived from synovial fringes.

In the hypertrophic variety of Charcot's disease osteophytic formation may also give rise to loose bodies, sometimes of great size.

Reference may be made here to the presence of a tuberculous sequestrum in a joint, although it cannot be classed as an osteophyte. Necrosis with separation of a fragment of bone is not characteristic of tuberculosis, in which rarefaction and caries are the rule, but it may occasionally occur, especially at the articular end of the femur. The process is probably due to interference with the blood supply, which explains the wedge-like form of the sequestrum. Such a sequestrum may form an osseous loose body in the joint.

Similarly, in acute arthritis there may be separation of part or the whole of an epiphysis, which comes to lie loosely within the joint. These two varieties of loose body are only included here for the sake of academic completeness.

2. *Traumatic Fragments in Normal Joints.*—It is feared that this title is a question-begging one, for very different views have been held regarding this, the classical form, of loose body in a joint. The recent work of Timbrell Fisher, however, has demonstrated that the majority of these cases are not due to a process of "quiet necrosis" gradually causing separation of a portion of the articular surface, as was suggested by Sir James Paget and others, but that the separation is due either to direct trauma or to muscular or ligamentous strain, either occasional or frequently repeated.

The general characteristics of such a loose body as outlined by Fisher are as follows. It occurs more frequently in males than females, and usually between the ages of 15 and 25. It is circular or oval in shape, about the size of an almond, and is plano-convex. The convex surface is smooth and has the typical appearance of articular cartilage, whereas the plane surface is roughened, although subsequent changes may smooth it down. Its com-

monest site is the knee, and then the elbow. In the case of the knee it is derived from the femur or patella, rarely from the tibia. It may be completely or incompletely detached, or may acquire a secondary adhesion to the synovial membrane. Its continual presence may lead to osteo-arthritic changes in the joint. It may undergo remarkable proliferative changes.

In recent cases the cells of the bony part of the fragment are alive. Were a quiet necrosis the cause of the separation the bone would be dead. The cartilage is hyaline articular cartilage, very different from the fibrocartilage of the osteophytic loose body.

In some cases the loose body, after remaining in the joint for a considerable time, may show evidence of proliferation. Cartilage is laid down around the original body, sometimes in an irregular nodular manner, sometimes concentrically. In one case described and figured by Fisher the body was 2½ inches in diameter, and the surface was extremely irregular and coral-like.

3. *Synovial Chondromata.*—Many years ago Kölliker showed that cartilage cells occur normally in the villous processes of the synovial membrane. It is but natural, therefore, that many loose bodies derived from synovial fringes should become converted into cartilage. It sometimes happens that these cells take on a true tumor growth, with the result that chondromata are formed.

Such chondromata may be single, but are frequently multiple. They may or may not be laminated. The number present may be remarkable. There is a specimen in the museum of St. Batholomew's Hospital showing 415 of these bodies removed from the knee joint, and James Berry has recorded a similar case in which no fewer than 1047 cartilaginous bodies were found in the knee joint of a woman 22 years of age.

The surface of the synovial membrane may be studded with these small cartilaginous nodules. Usually discrete, they may when compressed become caked into large masses. Microscopically they consist of hyaline cartilage.

TUMORS OF JOINTS

Synovial sarcoma is a rare tumor arising from the specialized connective tissue cells which line the sheath as well as from the deeper layer of fibrocytes. They often present a characteristic pseudoglandular structure by which their origin from the synovial layer may be suspected. The joint cavity is filled with soft, fleshy, vascular processes which seem to arise from many parts of the lining of the joint. The main feature of the microscopic picture is the differentiation of many of the connective tissue cells which become polygonal or cuboidal, whilst others remain flat and fusiform. The polygonal cells often surround a central cavity, giving a pseudoglandular structure. The spindle-shaped cells may become globular owing to marked mucoid degeneration. The polygonal cells may be arranged in nests suggesting epithelium, whilst in other areas the picture is sarcomatous. Synovial membranes have been regarded as reticulo-histiocytic tissues, and the tumor may present an appearance of a reticulo-histiocytosarcoma with cells which may be branching and anastomosing or may be syncytial in type, having a rich network of reticular fibrils that may surround individual cells. The tumor is radio-resistant and metasta-

sizes to the lungs. Similar synovial tumors grow from bursae and tendon sheaths.

Giant-cell tumors arise from joints and tendon sheaths. They resemble giant-cell tumor of bone, but are less destructive and are marked by the presence of numerous lipoid-filled xanthoma cells, so that they may be called xanthomatous giant-cell tumors.

CYSTS CONNECTED WITH JOINTS

There are three main varieties of such cysts. (1) The cyst may be due to a distension of a bursal sac which normally communicates with the joint. (2) The cyst may be formed by a pouch-like protrusion of synovial membrane through gaps in the capsular ligaments. These latter cysts were first described by Morrant Baker, and are known as Baker's cysts. (3) Cysts of the semilunar cartilages of the knee.

A *Baker's cyst* is usually found in connection with the knee joint. One of its important characteristics is its tendency to track through the tissues and thus recede from the joint. In this way the cyst may become so far removed from the joint that its nature is not recognized, and it may be opened on the assumption that it is a chronic abscess, the almost certain result being an infection of the joint. The distance to which these cysts may extend is sometimes phenomenal. I have dissected out one such cyst as far as the tendo Achillis (Fig. 512). Throughout most of its course it was very adherent to the surrounding tissues.

Fig. 512.—Baker's cyst which extended from the knee joint to the tendo Achillis.

Cysts of the semilunar cartilages nearly always affect external cartilage; involvement of the internal cartilage is very rare. The first cases in English were described by Ollerenshaw in 1921, but the condition is quite common. There is often a history of trauma. Mild pain and disability are the chief symptoms, and swelling on the outer side of the knee the chief physical sign. Part of the cartilage is converted into a cyst, which is usually multilocular with gelatinous contents (Fig. 513). In many of the cysts a definite lining can be detected. It seems probable that this is endothelial in character, being similar to that covering the synovial membrane. If this is so, it is probable that the cysts are developmental in nature, arising from portions of synovial membrane included in the semilunar cartilage. On the other hand it is possible that the cyst is the result of a gelatinous degeneration of the fibrocartilage, and that the lining is formed by modified fibro-

Fig. 513.—Cyst of external semilunar cartilage. (From Boyd, Text-book of Pathology Lea and Febiger, Publishers)

blasts. If this is correct, the cyst could be regarded as a kind of ganglion of cartilage.

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THE MUSCLES, TENDONS, AND BURSAE

THE MUSCLES

A voluntary muscle consists not only of muscle fibers but also of a fairly abundant interstitial connective tissue. It is this interstitial tissue which is involved in many of the pathological conditions affecting muscles, such as inflammations and neoplasms.

Atrophy.—Atrophy of a muscle may be due to three main causes: (1) disuse, (2) joint disease, and (3) nerve involvement.

1. Atrophy from disuse occurs whenever a muscle is not kept in full functional activity. Eventually almost all the contractile substance may disappear, and the muscle sheath becomes filled with fibrous and adipose tissue. There is no true reaction of degeneration.

2. Atrophy is a very constant accompaniment of joint disease, but frequently it is greater in degree than can be accounted for by mere disuse It may be, as first suggested by Paget, that impressions from the diseased joint pass up to the nerve cells in the anterior horn of the cord and there induce changes which give rise to what is really a neuropathic atrophy.

3. Atrophy of muscle will follow either interference with the motor nerve (probably owing to its containing trophic fibers), or disease of the motor cells in the anterior horn. Of such disease the best examples are acute anterior poliomyelitis and progressive muscular atrophy. In the earlier stages the muscle shows the characteristic reaction of degeneration. Later it becomes largely replaced by connective tissue and fat.

Congenital torticollis (wry-neck) is an interesting example of contraction due to fibrosis. Although it does not appear for months or years after birth it is due to injury to the neck muscles received at birth (Middleton). The contraction is limited to the sternomastoid muscle. The so-called "sternomastoid tumor," a spindle-shaped swelling which may appear from one to two weeks after birth, appears to be due to a temporary acute venous obstruction in the muscle during labor resulting in a hemorrhagic infarct of the muscle (Middleton). The obstruction is probably made permanent by a patchy intravascular clotting in the obstructed veins. The muscle fibers are replaced by young cellular fibrous tissue which is gradually changed into dense scar tissue. The reason for the late development of the wry-neck is that the neck of the infant is short. It is not until about the age of four that the individual changes from the "child" into the "small boy or girl," with marked growth of the neck in length. It is at this period that the fibrous contraction of the sternomastoid begins to pull the neck over.

Volkmann's Contracture.—This condition occurs in young people, affects principally the muscles of the forearm, and follows the use of tight splints or a tourniquet. Within a few hours the muscles lose their power,

and become swollen and very hard. Pain is usually present—due, perhaps, to an accompanying neuritis—but if absent the gravity of the condition may not be realized. Contracture of the fingers is an early sign. The muscles may show the reaction of degeneration. The contracture is permanent, varying in degree with the duration of the ischemia. If the muscle is exposed when the condition is fully developed it is hard, homogeneous, yellowish in color, and is not recognizable as skeletal muscle. Microscopically the muscle and cross striations are lost, and there may be an infiltration of inflammatory cells, and phagocytes at the margin of the area. Later the part becomes fibrosed.

Volkmann's original view was that the cause of the condition was ischemia due to direct pressure on the arteries. Later this was given up in favour of venous obstruction. The ischemic theory has now come back into its own, the ischemia being attributed to arterial spasm resulting from injury to the arterial wall (Griffiths). An identical picture, both pathological and clinical, can be produced in the rabbit by ligating the arteries to a limb.

Injury.—A muscle of a tendon may be injured by a direct blow, but rupture is frequently due to indirect violence, such as the sudden muscular exertion needed to regain the balance. Rupture commonly occurs at the junction between the muscle and its tendon. When rupture follows upon a comparatively trivial effort it may be due to the sudden contraction of the opposing muscles occurring before the affected muscle has had time to contract fully, as in the classical instance of a professional athlete who ruptured his biceps whilst sitting at table and endeavoring to catch a falling glass.

Blood is poured into the gap, and union takes place by the formation of fibrous tissue. No new muscle fibers are formed but there may be a regeneration of fibers as a result of outgrowths from the injured ends of healthy fibers. Millar's experimental study of this process in the young rabbit should be consulted. The healthy sarcoplasm forms an enlarged end or muscle bud. The nuclei proliferate, become enlarged, and come to lie in the center of the fiber. Two large nucleoli appear in each nucleus. The muscle bud grows into the wound, and myofibrils are laid down in the cytoplasm, which later develop cross striations. Muscle giant cells are formed by muscle segments no longer in connection with intact muscle; the nuclei multiply and there is increase of the sarcoplasm. The dead tissue is phagocytosed by histiocytes, which are so protean in form that they may be mistaken for new muscle cells. In the case of a ruptured tendon, new tendons may bridge the gap if it is not too wide.

Myositis.—Inflammation of muscle affects primarily the interstitial connective tissue. The muscle fibers are involved only secondarily, and they manifest degenerative rather than inflammatory changes. At no time a common condition, it may be due, (1) to the spread of infection from a neighboring focus such as an inflamed appendix, an empyema, an infected wound, and the like, or (2) to metastatic infection by the blood stream, especially in pyemia, typhoid fever, and gonorrhea.

The inflammation may be of any degree of intensity. There may be hyperemia and edema, fibrin formation, suppuration with abundant pus formation, or finally extensive gangrene and destruction. The last possi-

bility is most likely to occur when anaerobic organisms are present, especially when associated with much laceration of the tissues. It was only too common, therefore, in wounds of the muscles in the first world war.

The appearance of the affected muscle depends on the severity of the inflammation. At first it is red, swollen and sodden. Later it becomes of an unhealthy grey color, opaque, streaked with brown or yellow, with here and there areas of hemorrhage. Losing its normal firmness it becomes soft and friable, and if suppuration supervenes numerous pockets of pus are formed, and the pus may spread along the fascial planes. In the most severe forms, especially those due to anaerobes, the muscle becomes converted into a sloughing mass of greenish-black putrid material, which breaks down into a most evil-smelling dirty fluid.

In the milder cases resolution may occur. When the change has gone on to tissue death, healing must be accompanied by more or less extensive fibrosis. The abscess cavities must be shut off by granulation tissue, the contents become inspissated, and eventually lime salts may be deposited.

Acute Polymyositis.—This rare and obscure condition is one in which there is a severe non-suppurative inflammation of many muscles. The onset is usually gradual, with lassitude and pains in the muscles suggesting trichiniasis, but as a rule little or no fever. The muscles chiefly affected are those of the tongue, the back, and the limbs. The pain becomes so acute that the patient is unable to move in bed. The muscles are swollen, hard, and extremely tender. Death may occur from paralysis of the respiratory muscles with a resulting pneumonia. After a period of many weeks recovery may set in. The affected muscles are brownish-red, with areas of liquefaction, the fibers being degenerated and separated by round-celled infiltration. A characteristic feature is the presence of erythematous or urticarial patches on the skin, so that the disease has been called dermatomyositis. The condition is supposed to be due to an intestinal toxemia, but the evidence for this is not sufficient. It is probably a non-pyogenic infection of unknown nature.

Myositis Ossificans.—Although this condition is not really an inflammation it may be considered in this place. Bone may be formed in muscle in two classes of cases: (1) progressive myositis ossificans and (2) traumatic myositis ossificans.

1. *Progressive myositis ossificans* is a disease entirely obscure in its nature and universally fatal in its outcome. Commencing usually in childhood, it is often ushered in by an acute attack of pain associated with doughy circumscribed swellings in one or more groups of muscles, especially those of the back and neck. The further progress of the disease is by fits and starts, periods of remission being followed by aggravation of the symptoms. The affected areas gradually become calcified and converted into bony plates, until the body becomes enveloped in a rigid cuirass which renders all movements impossible, the pitiable condition being terminated by some pulmonary complication.

In one case which I had an opportunity of studying, and which has since been published by A. P. MacKinnon, the appearance of the back suggested the ridges on a relief map. Great masses of bone could be felt in the latissimus dorsi on both sides, in the deltoid, the brachialis anticus, and the triceps; a kind of poker passed from the mid-dorsal region to the

sacrum, joining the spinous processes, and a bony band, an inch and a half wide, extended on each side from the os pubis to the upper part of the femur along the line of the upper margin of the abductor magnus; the rectus femoris and the muscles of the leg were also involved. Needless to say, the X-ray picture was bizarre in the extreme (Fig. 514). The patient was a young man of nineteen, and the disease made its first appearance at the age of fifteen.

The condition appears to be at first an inflammation of the connective tissue of the muscle, and in the granulation tissue thus formed true ossification then occurs. It would almost appear that some congenital anomaly plays some part in the causation, for not only does the disease appear in

Fig. 514.—General myositis ossificans affecting the muscles of the back.

early childhood, but other congenital defects such as microdactyly in the hand and absence of a phalanx of the great toe are very constantly present.

2. *Traumatic myositis ossificans* (Fig. 515) may occur as the result of repeated injury to a muscle, but occasionally it may follow a single trauma, such as the kick of a horse on the thigh. Repeated bruising of the adductor longus in cavalry soldiers may be followed by the development of a bony mass, the so-called rider's bones. The blow of the butt of a rifle on the pectoral muscle may give rise to a similar condition. Dislocation of the elbow may be accompanied by a bony formation in the brachialis anticus. In myositis ossificans the area is well defined, and there is a definite interval between the mass of new bone and the bone itself. Hematoma appears to be an important antecedent. The stimulus to ossi-

fication is probably chemical; there is increased deposition of calcium in the presence of an injured blood supply. In some cases, however, there may be detachment of osteoblasts from the periosteum as the result of the trauma. It is important not to confuse new periosteal bone formation encroaching on and displacing muscle with true myositis ossificans.

Fibrositis of Muscle.—There is a group of conditions in which the principal symptom is sudden and severe pain when a muscle is contracted. Some of the best-known examples are lumbago, affecting the muscles of the lower part of the back; stiff-neck, affecting the sternomastoid; and pleurodynia, affecting the intercostal muscles. It is to this class of case that the vague and unsatisfactory term of muscular rheumatism used to be applied.

For long it has been presumed that the underlying lesion responsible for the pain is a subacute or chronic inflammation of the connective tissue of the muscle involving the nerve endings. Such lesions have never been demonstrated in excised portions of tissue.

Important new light has been shed on the question of so-called fibrositis of the back by the work of Copeman and Ackerman in 1944. They showed that the lesions apparently responsible were herniations of certain fat lobules through weak spots or actual deficiencies in the walls of their investing fibrous tissue. (Fig. 516.) The herniation may be congenital in nature through well-defined gaps in the fascial layers, or may be acquired as the result of mechanical strain. Everyone knows how sudden crippling pain in the back may follow a simple exercise such as digging, or so

Fig. 515.—Myositis ossificans; new bone formation in muscle. × 136.

trivial an exertion as stooping down to pick up a golf ball, as happened to the writer on one occasion. No other hypothesis serves to explain these puzzling cases, where the onset of the pain is as sudden as the lash of a whip, as does that of herniation of fat lobules. It is probable that the pain may be maintained and intensified by such secondary changes as edema of the fatty tissue, hemorrhage, congestion, or torsion of the pedicle of the prolapsed lobule. Herz and also Mylechreest have shown that complete cure or striking relief may be afforded by removal of the fatty hernias. It is well known that temporary relief follows the injection of local analgesics into the affected area.

Tuberculosis of Muscle.—Tuberculous disease of muscle may occur in two forms: (1) it may be due to extension from a neighboring focus in bone, glands, or pleura; (2) it may be primary, that is to say it may be metastatic due to blood spread from some preexisting distant focus. The latter form is very rare, whilst the former frequently occurs from disease of the vertebrae, the hip joint, or the lungs.

A tuberculoma is first formed in the muscle presenting the usual histological appearance. Caseation occurs with the formation of a cold abscess, which may appear at a great distance from the initial lesion. The behavior of such a tuberculous abscess has already been considered in Chapter II.

Tumors of Muscle.—Tumors of striated muscle are very rare. There are two main forms arising from muscle cells, the rhabdomyoma and the myoblastoma. The primitive muscle cell or myoblast is first oval and later elongated; longitudinal striations then appear and finally transverse striations. The *myoblastoma* is a tumor consisting of round or elongated cells in ribbons or bundles; they have the strongly acidophilic cytoplasm of muscle fibers, but no transverse striations, or only very faint striations shown by iron hematoxylin staining. There may also be the large multinucleated syncytial masses seen in the healing of injured muscle. The most characteristic feature of the cells is their markedly granular cytoplasm, so that they have been called granular cell myoblastoma. It is by no means certain that these tumors arise from myoblasts, for they have been found in sites devoid of striated muscle, as well as in the substance of such
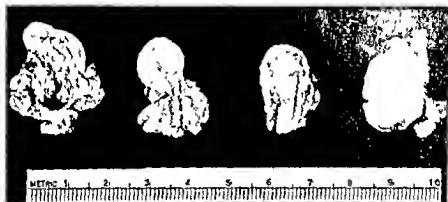
Fig. 516.—Fat lobules removed from patient with chronic lower back pain.

muscle. The common sites are the tongue, larynx and skin, but it has also been found in the lip, upper part of the esophagus, and leg. The tumor is usually benign, but malignant forms have been described. The *rhabdomyoma* consists of fully striated fibers. In spite of this differentiation the tumor is more malignant than the myoblastoma. The purest form occurs in the heart, but it is also found in the palate, bladder, vagina and cervix. The tumors growing on mucous surfaces, such as bladder and vagina, tend to be lobulated and polypoid.

Fibroma.—The only variety of fibroma which calls for special notice is that which occurs in the anterior abdominal wall, especially in the rectus abdominis, to which the name *desmoid tumor* is given. It occurs in women in 90 per cent of cases, and usually in those who have borne children. These tumors are mildly fibrosarcomatous, for they tend to recur locally when removed, so that Paget called them "recurrent fibroids." They are densely hard, and interlacing bands of fibrous tissue are seen on the cut surface (*desmos*, a band). The enclosed muscle fibers may become converted into multinucleated plasmodial masses like giant cells.

Angiomas.—Whilst not common, these tumors are of importance, for, although characterized by pulsation, a thrill, a murmur, and the youth of the patient, they may be mistaken for other forms of tumor with unpleasant results. I once entered an operating room to find the place swimming with blood, the surgeon having mistaken an angioma of the popliteal space for a fatty tumor. The muscles of the calf were so infiltrated by the growth that the leg had to be amputated.

Sarcoma.—Primary sarcoma of muscle is rare. Secondary growths are distinctly common.

Carcinoma.—This is of course always secondary, and is far from common. There is a specimen in the University of Manitoba Pathological Museum of a large epitheliomatous mass in the flexor muscles of the forearm, secondary, apparently, to an epithelioma of the lip, a remarkable site for a metastasis in a tumor which rarely sets up any distant metastases.

Trichiniasis.—The embryos of the trichina are carried from the bowel to the muscles, especially the flat muscles, by the blood stream. An embryo enters a muscle fiber, becomes curled up, dies, and is surrounded by a fibrous capsule. The nodule becomes calcified. The stage of invasion is marked by severe pain and swelling of the muscles, fever, and other constitutional symptoms. The blood shows a well-marked eosinophilia.

Hydatids.—Hydatid cysts of the muscles occur in less than 2 per cent of cases of hydatid disease. They may form tumors as large as a hen's egg. Calcification usually occurs, so that a hard calcareous mass is formed.

THE TENDONS

Tenosynovitis.—Inflammation affects the sheath of a tendon to a much greater extent than the tendon itself, so that the condition is known as tenosynovitis. The inflammation may be due to: (1) trauma, (2) pyogenic infection, (3) gonorrhea, (4) tuberculosis, (5) syphilis, and (6) gout.

Traumatic Tenosynovitis.—This occurs in those in whom the tendons are subjected to excessive use, as in piano-players. Considering the comparative infrequency of the condition it is probable that some other factor, possibly toxic, comes into play.

As in the pleural cavity, the inflammation may be dry or moist. In the dry form a deposit of fibrin is laid down upon the tendon and the walls of the sheath, producing a most characteristic symptom of creaking or crepitation similar to the friction of dry pleurisy. The breaking down of adhesions, which are so apt to form and which produce considerable disability, has made the reputation of many a bone-setter. When effusion occurs the crepitation naturally disappears, and an elongated swelling appears in the long axis of the tendons. The tendons most frequently affected are the extensors of the wrist and the thumb, the peroneal and extensor tendons of the ankle, and the tendo Achillis.

Suppurative Tenosynovitis.—This is the result of the spread of infection in the neighborhood. The most frequent cause is a whitlow of the fingers. As the tendon sheaths of the thumb and little finger are continuations of the flexor sheath in the forearm, infection of these digits is more far-reaching in its consequences. Abundant granulation tissue is formed within the sheath, so that firm adhesions may result. When the inflam-

mation is more severe the tendons, which are very poorly supplied with blood, may slough.

Gonorrheal Tenosynovitis.—This is usually a mild inflammation, but it may be severe. In the mild form there is serous effusion into the sheath, giving rise to an elongated swelling, or no effusion may occur, there being merely pain and disability. In the severe form the inflammation may be so acute as to go on to suppuration. Even in that case, however, the tendons rarely slough. The tendon sheaths principally affected are those of the wrist and ankle.

Tuberculous Tenosynovitis.—Tuberculosis of the tendon sheaths closely resembles tuberculosis of joints. It may, therefore, be primary in the tendon sheath, or may be secondary to bone disease. As with tuberculous arthritis, there are two main forms; in the first there is a diffuse and abundant formation of granulation tissue, in the second there is hydrops with the production of melon-seed bodies.

The *fungous* variety is analogous to the tuberculous white swelling of joints. The synovial sheath is filled with soft pulpy granulation tissue studded with tubercles. This undergoes caseation, and may break down and liquefy. This form is usually due to extension from a neighboring bone focus.

The *hydrops* form is characterized by an abundant serous effusion into the sheath. A limited amount of tuberculous granulation tissue is formed, on the surface of which a layer of fibrin is deposited. Owing to the friction of the tendon much of this fibrin becomes detached and converted into the little rounded masses known as *rice-bodies* or *melon-seed bodies*, which give a very characteristic crepitant sensation when the swelling is palpated. This is the condition which used to be called a compound ganglion. The sheath may be packed full of the melon-seed bodies (Fig. 511).

The tendon sheaths most commonly involved are the common flexor sheath of the wrist and the peroneal and extensor sheaths at the ankle. At the wrist the swelling is hour-glass shaped, owing to the constriction of the annular ligament.

Syphilitic Tenosynovitis.—In the secondary stage of syphilis a mild tenosynovitis may develop. In the later stages gummata of the tendon sheaths may occur.

Gouty Tenosynovitis.—In gouty patients there may be deposits of urate of soda in the tendon sheath or beneath the synovial covering of the tendons. These may give rise to nodular masses which can be felt to move with the tendon, and which may cause a considerable amount of irritation.

Tumors of Tendon Sheaths.—The ordinary tumors of connective tissue occasionally occur in the tendon sheaths, and are very liable to be mistaken for tuberculous disease. A lipoma arising from the synovial membrane often follows the course of the tendons, and at the wrist may give rise to a branching tumor.

Synovial sarcoma of tendon sheaths is identical with the similar tumor in joints (see page 769).

Reference may be made to the *giant-celled tumor* which occurs at the wrist or at the attachment of the tendon to the phalanx. This forms a firm mass of no great size, and is composed mainly of multinucleated

giant cells. The structure is the same as that of the giant-celled epulis. There may be numerous xanthoma cells filled with lipoid material which gives a foamy appearance to the cytoplasm. The tumor appears to arise from the cells of the synovial membrane of the sheath.

Ganglion.—A ganglion is a cystic swelling occurring in connection with a tendon sheath, especially in the neighborhood of a joint. The three principal sites where they occur are the back of the wrist, the dorsum of the foot, and the outer aspect of the knee. Of these the wrist is by far the commonest position.

The size varies from that of a pea to that of a plum. On the wrist it is usually rather soft, becoming tense when the wrist is flexed. On the foot it is more hard and tense, and is apt to be mistaken for a tumor. At the knee it may be confused with a bursa or a synovial cyst.

The capsule consists of dense fibrous tissue continuous with the surrounding connective tissue and especially with the tendon sheath. There is no endothelial lining, so that the fibrous capsule is in contact with the contents. The latter are clear and jelly-like.

The mode of formation is by no means clear. It used to be thought that the ganglion arose as the result of the protrusion through the fibrous capsule of the synovial lining of the tendon sheath or the joint. In most cases, however, no communication can be found between the ganglion and the tendon sheath, and even where such a communication does occur it appears to be secondary rather than primary. It is more probable that the connective tissue of the sheath undergoes proliferation followed by mucoid degeneration with the formation of a number of small cysts which eventually fuse into one large cavity. The essential reason for these changes is unknown.

The condition formerly known as *compound palmar ganglion* is not a true ganglion, but a tuberculous inflammation of the tendon sheaths at the wrist.

Dupuytren's Contraction.—It was in 1831 that Dupuytren gave the first description of what he called "permanent contracture of the fingers." The most striking lesion is an extreme degree of thickening and hardening of the palmar fascia, which is shortened and under tension. This lesion, which is progressive, causes the fingers to be flexed on the palm, and renders normal use of the hand impossible.

The etiology has long been a matter of debate. The extensive studies of Meyerding and his associates suggest that the condition is an inflammatory one involving the skin, subcutaneous tissue and interstitial connective tissue down to the tendon sheaths. The palmar fascia is remarkable for the fact that within its fibers there is evidence of an active proliferation of fibroblasts without other signs of inflammation, an appearance which may be mistaken for fibrosarcoma. The sarcoma-like areas are situated in nodules which are a characteristic feature of the palmar fascia. In the subcutaneous tissue there is disappearance of fat and sweat glands, which are replaced by fibrous tissue.

THE BURSAE

A bursa is a sac lined by synovial membrane and containing synovial fluid. Similar as it is in structure to a joint and a tendon sheath, it is

equally similar in the diseases to which it is liable. Many bursae are pre-existing, but others, called adventitious bursae, are developed as the result of friction. Most bursae are closed sacs, but a few communicate with a joint cavity; that, for instance, between the gastrocnemius and the semimembranosus is usually continuous with the knee joint.

The principal pathological condition affecting a bursa is inflammation. This may be due to trauma, to infection, or to tuberculosis.

Traumatic bursitis may be the result of a blow, such as a fall on the knee (prepatellar bursa), the elbow (olecranon bursa), or the shoulder (subacromial bursa). More frequently, however, it is due to chronic irritation, as seen in the "housemaid's knee" or the "student's elbow." A condition of hydrops develops, the bursa being distended with serous fluid, sometimes to an extreme degree.

When the condition is of long standing the wall may undergo great thickening, and becomes covered by fibrous ridges, septa, and tags (Fig. 517), so that the appearance somewhat resembles the interior of a joint the seat of chronic arthritis. The tags may become detached and form melon-seed bodies, which can be detected on palpation. Occasionally the thickening is so great that the cavity is almost obliterated, and the bursa becomes converted into a solid mass.

Infective bursitis is usually due to infection introduced by a perforating wound. Sometimes, however, it is the result of the extension of inflammation from the neighboring joint or bone. The olecranon and prepatellar bursae are the most frequently affected, and become distended with pus, which may rupture the wall and pass for some distance along the limb.

Fig. 517.—Bursa showing effects of chronic inflammation. The wall is covered by numerous tags, and fibrous bands transverse the cavity.

Rheumatism and gonorrhea may give rise to inflammation of bursae, especially in the subacromial bursa and in the bursa between the tendo Achillis and the os calcis.

Tuberculous bursitis is similar to tuberculous tenosynovitis. There may therefore be hydrops with melon-seed bodies, or an abundant formation of tuberculous granulation tissue with subsequent softening and liquefaction. The disease may be primary in the bursa or secondary to bone or joint tuberculosis. Any bursa may be affected, but special reference may be made to the subacromial bursa, owing to the difficulties of diagnosis which it may present unless the condition be kept in mind.

Tumors of bursae are of the same type as tumors of tendon sheaths (see page 779). The chief of these are synovial sarcomas and giant-cell tumors. The *synovial sarcoma* already described in connection with joints (see page 769) may arise from bursae.

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CHAPTER XXXIII

SURGICAL PATHOLOGY OF THE THORAX

The last quarter of the nineteenth century saw the development of the surgery of the abdominal cavity, the first quarter of the twentieth century the development of the surgery of the cranial cavity, and the second quarter of this century the development of the surgery of the thoracic cavity. In 1895 Reclus, addressing the French Surgical Congress, remarked that "resection of a part of the lung for primary malignant disease is not even worth discussing." In that same year Stephen Paget declared with regard to surgery of the chest that it is "utterly untrue that surgeons fifty years hence will think as little of our results as we think of the methods of fifty years ago." The existence today of journals, societies and tumor registries devoted solely to thoracic surgery demonstrates how dangerous is the role of the prophet.

The two lungs are completely separated from each other by the mediastinum so that the two pleural cavities are independent. But from the surgical standpoint the cavities and their contents cannot be considered individually. When one lung or a part of one is removed the mediastinum and the other hemithorax will be affected. The mediastinum is not a rigid partition but a mobile structure; yet in health it is so balanced by the elasticity of the lungs on either side as to be practically devoid of movement. Changes in the contents of the thoracic cavity tend to cause displacement of the mediastinum and heart. These structures return to their normal position during inspiration, but are displaced once more on expiration. This movement is slight with quiet respiration, but if an opening is made in the chest wall, the mediastinum and heart may flap to and fro with every respiration, causing severe cardiac and respiratory embarrassment. Modern advances in thoracic surgery, including refinements in differential pressure anesthesia, have largely solved these problems. As the result of disease the mediastinum may become more rigid and therefore less mobile.

TUMORS OF THE LARYNX

Papilloma.—This is the commonest tumor of the larynx, occurring particularly in singers and those who use the voice much. It is a small warty growth composed of loose connective tissue arising from the vocal cords or the anterior commissure. In the adult it shows a strong tendency to recur after removal, and may rarely become malignant. In children there is also a strong tendency to apparent recurrence, but the new tumors are often in a different location from the initial one, and there is a tendency to spontaneous cure, so that it is a self-limited disease.

Carcinoma.—Stratified squamous epithelium covers the true vocal cords, the laryngeal side of the epiglottis, and the anterior surface of the ventricles. Beyond this it shades outwards into a stratified columnar cili-

ated epithelium with lymphoid cells in the stroma. Corresponding with this change in structure there is a change in the type of carcinoma and in its radiosensitivity, the latter increasing as we pass outward from the laryngeal box. Two forms of carcinoma occur, which are known as intrinsic and extrinsic. Quick points out that the intrinsic form should be called carcinoma of the larynx, whereas the extrinsic form is really carcinoma of the hypopharynx. The *intrinsic* form constitutes 80 per cent of the cases, and arises from the vocal cords, usually the anterior third. The tumor, originating from fully differentiated stratified squamous epithelium, often remains confined to the larynx for a considerable time, for the larynx proper has very meager anastomosis of lymphatics with the neighboring parts. There is, therefore, a good chance of recovery after operative removal. The *extrinsic* form arises in the pyriform fossa, the aryepiglottic folds, or on the epiglottis. It involves the hypopharynx, invades the surrounding tissue owing to the abundant lymphatic drainage, and gives rise to early lymph node metastases. The intrinsic form is epidermoid, the extrinsic form usually transitional in type and is markedly radiosensitive.

Carcinoma of the larynx is far commoner in males than in females, and often shows a definite relation to chronic irritation, such as overuse of the voice or abuse of tobacco and alcohol. It begins as a small indurated patch or as a papillary tumor. In the later stages there is extensive destruction, ulceration, and sepsis with the danger of lung abscess or inhalation pneumonia.

TRACHEA AND BRONCHI

The chief surgical lesions of the trachea and bronchi are benign and malignant tumors and bronchiectasis. The latter might equally well be considered in connection with the lungs, for it is the intrapulmonary portion of the bronchi which is involved.

Benign Tumors.—Benign tumors of trachea and bronchi may be epithelial or connective tissue in type. In the *trachea* there may be papilloma (usually in children and multiple in type), fibroma, or lipoma. The connective tissue tumors are often mixed. I have studied one such tumor which completely filled the trachea and microscopically could be described as fibrosarcoma xanthomatosum, the cells being loaded with doubly refractive lipoid.

In the *bronchi* the chief tumors are adenoma, fibroma, and lipoma. Mixed fibrolipomas have been reported. The only tumor which needs to be discussed in detail is the adenoma.

Bronchiectasis.—Bronchiectasis is a dilatation of the bronchi, either local or general. The condition used to be regarded as comparatively rare, but with modern methods of diagnosis it has become apparent that in its milder forms the disease is a very common one, and many cases which used to be regarded as chronic bronchitis of an intractable character are now known to have a bronchiectatic basis. Much of this change has been due to the introduction of lipiodol in X-ray technique. The disease is far less responsive to purely medical treatment than is pulmonary tuberculosis; indeed, there is no medical cure. Remission and relapse are natural phenomena of the disease, and medical treatment is often given the credit for what are merely natural remissions. It is a pity that it is not known to the public by some simple and descriptive name as "lung rot," for then

its dire consequences would be better appreciated. Riggins describes the morbidity of advanced cases as "consisting of chronic invalidism, psychological changes varying from mild depressive states to psychopathic personalities, complete economic instability, a life alone, apart, helpless and hopeless." The morbidity, indeed, is a greater problem than the mortality, and suicide may end the history of the case.

Etiology.—The two main factors are infection of the bronchial wall and increased intrabronchial pressure as the result of coughing. In these respects it is strictly analogous to aneurism. Robinson, examining a large number of fresh specimens removed surgically in the Toronto General Hospital, finds that the most constant lesion is a chronic inflammation of the bronchial walls with varying degrees of damage up to complete destruction of the musculo-elastic tissue. This destruction, as in syphilitic aortitis, leads to dilatation of the affected segment of the bronchial tree. The dilatation favors accumulation of secretion, with added infection, and further injury to the bronchial wall, so that a vicious circle is established. X-ray studies of the normal animal lung by means of a barium mixture have shown that the bronchi are not the rigid immobile tubes we are apt to picture them. The bronchi become longer or shorter, and a wave of peristalsis passes along the entire tube. The picture on the screen is thus living and animated. Normal drainage of pulmonary secretions is probably brought about in this way, a self-cleansing of the smaller bronchi which is hopelessly impaired in bronchiectasis. It is only when the secretion reaches the main bronchi that the cough reflex, the watch dog of the lung, is excited. In bronchiectasis the secretion has been shown to remain in the damaged bronchi for weeks or months. Erb believes from examinations of material from the Hospital for Sick Children, Toronto, that the essential primary lesion is an acute *ulcerative* bronchitis with secondary destruction of the bronchial wall and extension of the process into the surrounding lung. The difference in viewpoint is to be explained by the difference in the material examined; in young children the process tends to start more acutely and give rise to more immediate destruction.

No one organism is responsible for the bronchial infection. The virus diseases such as measles, influenza and whooping cough (a possible virus infection) are often the starting point, but the ordinary bacterial respiratory infections are frequently responsible. In both of these cases there is usually a history suggesting bronchopneumonia. The great majority of cases begin in childhood or adolescence, although the condition may not be recognized till adult life. Sinus infections with continued seepage of septic material into the bronchial tree have naturally been blamed, but such infections arise at a later age period, and it seems probable that they are a result rather than a cause of bronchiectasis. Congenital defects in the development of the bronchial tree have been suggested as a basis of the condition, but the evidence in support of this idea is not convincing. Traction on the bronchial walls by fibrous tissue formed as the result of bronchopneumonia is always mentioned, but this appears most unlikely.

Bronchial obstruction is almost certain to lead to some degree of bronchiectasis, owing to the infection which results from interference with normal drainage. Such obstruction may be caused by adenoma, or carcinoma, a foreign body lodged in the bronchus, tenacious sputum in the

lumen, or pressure from outside. In children, in whom the bronchi are easily compressed, the pressure may be due to enlarged tuberculous lymph nodes, and in adults it may be due to tumor or aortic aneurism. A further discussion of these matters will be found in Warner's excellent review.

Morbid Anatomy.—The dilatation is usually diffuse (cylindrical) (Fig. 518), but it may be localized (saccular). The lower lobe is involved much more frequently than the upper, the left more often than the right. The disease is unilateral in about one-half of the cases, and in one-quarter it is restricted to one lobe. The cavity may be as large as an orange if it is formed from the larger bronchi, or as small as a pea if originating in the bronchioles. The mucosa at first is much thickened and may project into the lumen as papillary masses which are highly vascular, so that hemoptysis occurs in 50 per cent of the cases. Later, atrophy succeeds hyper-

Fig. 518.—Marked and widespread bronchiectasis, lobectomy specimen

trophy. The contents of the cavity are purulent but not necessarily fetid, depending on secondary infection with anaerobic putrefying bacteria. When such infection occurs the breath acquires an extremely offensive odor. The formation of secondary lung abscesses is rare. When it does occur the abscess cavities are likely to be in healthy parts of the infected lobe, due to a spilling over of septic material. In advanced cases the bony cage is fixed in a position of deep inspiration, and the diaphragm is flattened, so that the pulmonary reserve is seriously depleted.

The *microscopic picture* as in syphilitic aortitis is a combination of inflammation and destruction of tissue (Fig. 519). The wall is infiltrated with chronic inflammatory cells, and in advanced cases the glands, muscle, elastic tissue and even the cartilage may have disappeared and been replaced by fibrous tissue. The epithelial lining is retained in a remark-

able manner, although in places it may be missing. Perforation of the bronchial wall may occur. The vessels in the wall may be greatly dilated, so that hemoptysis is a frequent symptom. If these veins become thrombosed, the thrombus may form an infected embolus giving rise to metastatic abscess of the brain. As attacks of bronchopneumonia are frequent, the surrounding lung parenchyma is usually fibrosed, with compensatory emphysema in the more peripheral zones.

Congenital Bronchiectasis.—It sometimes happens that a child suffers from severe recurrent attacks of dyspnea and cyanosis quite early in life. One of these attacks may end fatally, and at autopsy it is found that the lung presents many cyst-like cavities, so that the condition is often called *congenital cystic lung*. The recurring attacks of dyspnea and cyanosis are due to rupture of a superficial cavity, with resulting pneumothorax. The cysts are lined by a layer of epithelium, which may be flattened or cuboidal; some-
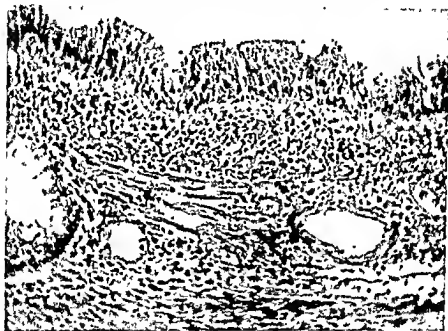
Fig. 519.—Bronchiectasis: muscle and elastic tissue replaced by inflammatory exudate, epithelium intact. × 160.

times it is ciliated. In one case which I studied, the elements of the bronchial wall could be readily recognized. The condition must be regarded as a congenital dilatation of the small bronchioles, even though most of the cysts may be closed and fail to communicate with the bronchi. There may be marked pulmonary hypertension as a result of vascular occlusion. In my case the pulmonary artery was enormously dilated so that it resembled a fusiform aneurism. It measured 12 cm. in diameter, whereas the aorta at the same level measured only 7 cm.

Adenoma of the Bronchus.—These tumors have only attracted surgical attention within recent years, for it was only in 1932 that they were first recognized clinically. They are almost always situated in one of the large bronchi. In contrast with bronchial carcinoma they occur for the most part before the age of 40, and over half the cases are in females. In the earlier literature they appear under a bewildering variety of names, and

indeed new names continue to appear, an indication of the wide variation in structure and of the different interpretations which have been put on that structure.

The probable origin is from the mucous glands of the bronchial wall or their ducts, although other opinions are held by excellent observers. The growth is both into the lumen and into the wall of the bronchus, and, like an iceberg, the hidden or exobronchial portion may be much larger than the endobronchial portion visible to the bronchoscopist. Whilst removal of the endobronchial part will relieve the obstruction, it is evident that there is always danger of recurrence which may have to be treated by more radical measures. The endobronchial portion may be smooth or present a raspberry-like appearance (Fig. 520). The expansion and outward growth of the tumor leads to pressure atrophy of the bronchial wall which may be mistaken for true invasion. For practical purposes the tumor

Fig. 520.—Adenoma of bronchus.

Fig. 521.—Adenoma of bronchus. × 320

can be regarded as benign or of very limited malignant tendencies, although in rare instances spread to the regional lymph nodes has been recorded. An adenoma may become carcinomatous, so that removal by lobectomy is advisable.

The *microscopic picture* is marked by its variability of form. The cells are small, cuboidal or polygonal, with a dark nucleus. They are grouped in a variety of patterns which may be alveolar, columnar, medullary or mosaic in type, depending on the arrangement of the reticular stroma which divides the cells into groups (Fig. 521). Unless these characteristic patterns are present, microscopic diagnosis from material removed by the bronchoscope may be by no means easy. The surface cells may undergo squamous metaplasia which may suggest epidermoid carcinoma Many of the tumors are highly vascular, thus explaining the severe hemoptysis which is the most characteristic symptom. Occasionally meso-

blastic elements are present, including osteoid tissue, cartilage and bone. It has been suggested that these tumors arise from embryonic bronchial buds which fail to develop, and that they should be classed as "mixed tumors," similar to those which occur in the salivary glands (Womach and Graham). It seems more probable that the mixture is to be explained on the same basis as that found in salivary gland tumors, namely, a gradual change of epithelium through myxomatous and mucoid tissue into pseudocartilage or true cartilage. The attributes of a cell depend in part on the dictates of its environment, and if a cell is sufficiently immature it possesses a plasticity which enables it to be molded by that environment. It may be said in general that the microscopic picture looks more malignant than it really is, thus explaining such terms as alveolar sarcoma, basal-cell carcinoma and adenocarcinoma which have been applied to it.

The cardinal symptom, as already mentioned, is hemoptysis. This is often profuse, and is as sudden in its termination as in its onset. In one case which I studied the patient suffered from occasional attacks of hemoptysis over a period of twenty-five years. In women the attacks may coincide with the menstrual periods. As the tumor slowly fills the lumen of the bronchus, obstructive effects develop as in bronchial carcinoma, so that the clinical picture may be one of atelectasis, bronchiectasis, or lung abscess.

Carcinoma.—Many names have been given to carcinoma of the lower respiratory tract, e. g., primary carcinoma of the lung, bronchial carcinoma, bronchogenic carcinoma and bronchiogenic carcinoma. Any one of these can be used, for all are correct, except perhaps the first. Bronchial carcinoma (or carcinoma of bronchus) is the simplest, and corresponds with gastric or renal carcinoma, but bronchogenic carcinoma has established itself as the popular term. Its original justification was that it emphasized the origin of the tumor from a bronchus rather than from the lung, but such emphasis is no longer necessary.

Incidence.—The most interesting single fact about this disease is that it passed from being one of the rarest forms of carcinoma to being one of the most common. The opening sentence of Adler's book on the subject, published in 1912, is as follows: "Is it worth while to write a monograph on the subject of primary malignant tumors of the lung?" The references in a paper by Ochsner and DeBakey on this subject written in 1941 cover 16 pages. Adler continues in his first paragraph: "On one point, however, there is nearly complete consensus of opinion, and that is that primary malignant neoplasms of the lungs are among the rarest forms of disease." During a 15-year period ending 1940 in the Department of Pathology at the University of Toronto, the third most frequent site of primary carcinoma in autopsy material was the lung, being surpassed only by the stomach and large bowel, and in my material at Winnipeg the incidence was even higher. The increase is world-wide, as shown by reports from all civilized countries.

This remarkable increase has been the topic of endless discussion under two headings, first as to whether the increase is real or only apparent, and second as to its explanation if it is real. The consensus is that it is real. The increase then has to be explained, for in no other form of carcinoma is there a similar world-wide increase in incidence. The explanations ·

are remarkable for their ingenuity. Suspicion has been especially directed against automobiles and their exhaust gases, as these have become a new element in life in the period under consideration. Mention is always made of the tarring of roads, because lung carcinoma can be produced in mice and guinea-pigs by the intratracheal insufflation of coal tar. But the disease is as prevalent in the great open spaces of the western prairies, whose roads are untarred and there are few automobiles, as it is in the large cities. It is as common in Russia and Syria as it is in New York and Pennsylvania. Were automobile exhaust gases of any importance the disease would be rampant amongst garage workers, but it is not. Nor are employees in tar works liable to the disease, so that there is no analogy with aniline dye cancer of the bladder. It has been suggested that cigarette smoking, which in pandemic form is of recent origin, is the etiological factor, but this fails to explain the low incidence in women, who are amongst the most inveterate of smokers. The pandemic of influenza in 1918–1919 used to be blamed, but that is as distant as the first world war.

Of all the facts in supposed relation to the etiology of the disease which burden the literature, the only one of real significance is the "Schneeberg lung cancer." For many centuries (ever since A.D. 1500) it has been known that one of the commonest causes of death among the workers in the cobalt mines in Schneeberg, in Saxony, was a mysterious lung disease characterized by cough, dyspnea, loss of weight, pain in the chest, and mucopurulent or bloody sputum. This was considered to be tuberculosis, and later silicosis. In 1922 an official investigation under the leadership of Schmorl was instituted which lasted for 3 years. Autopsy examination disclosed the startling fact that 71 per cent of the deaths amongst miners during that period were due to cancer of the lung. No example of the disease was found in persons living in the same district, but not working in the mines. It is evident that the miners were exposed to a carcinogenic agent, possibly mechanical, possibly chemical, most probably a radioactive emanation, for cancer of the lung is also prevalent amongst workers in the highly radio-active neighboring mines at Joachimsthal.

My own opinion is that the increase in the incidence is mainly, perhaps entirely, apparent rather than real. The clinician has been shown by the pathologist that the basis of a certain clinical picture is carcinoma of the lung, so that a correct diagnosis can now be made in a large majority of cases, although many are still uncovered only in the autopsy room. The radiologist has greatly added to the number of cases successfully diagnosed, for he no longer looks for a clean-cut tumor such as is seen in secondary carcinoma, but for displacement of the mediastinum, atelectasis, bronchiectasis, pleural effusion, and other effects of lung carcinoma. The bronchoscopist, being a new arrival in the field, is responsible for a further increase in the numbers of cases. The failure of skilled pathologists in the past to recognize the condition is an apparent stumbling block to the acceptance of this view. The reason is probably contained in Goethe's saying: "Was man weiss, sieht man," what one knows one sees. The Schneeberg lung disease had been observed for 400 years, but only since 1922 was it recognized to be carcinoma of the lung. The failure of the pathologist was due to the fact that he was not familiar with the usual gross appearance, the microscopic picture, and the natural history of

the disease. Now that these have been recognized, anyone can make the correct diagnosis in the autopsy room.

Gross Appearance.—The gross appearance varies greatly. From the surgical standpoint a convenient classification is that suggested by Rabin and Neuhof. They divide the tumors into two main groups, circumscribed and non-circumscribed. The latter, which unfortunately constitute 75 per cent of the cases, are hilar in position and arise from the main bronchi. The circumscribed form constitutes 25 per cent of the cases according to Rabin and Neuhof, although in my own experience the group is a good deal smaller. About half of these form compact spherical tumors with no visible relation to macroscopic bronchi; they grow by expansion rather than invasion, lymph spread is not a marked feature, and death is due to
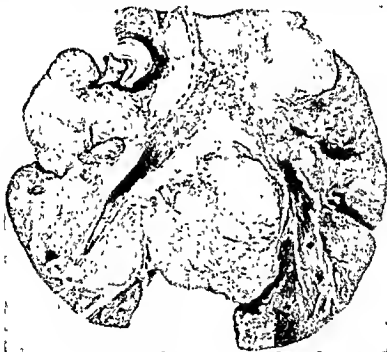
Fig. 522.—Carcinoma of bronchus showing roughening of mucosa, outward spread and massive involvement of lymph nodes.

distant blood-borne metastases. The other half of the circumscribed group remain limited on the central aspect, but spread peripherally to the pleura, invading the chest wall and destroying the ribs.

In the common hilar form a papillary mass may project into the lumen of a large bronchus, in which case it is easily recognized as the similar form of carcinoma of the stomach. Much more frequently, however, the growth is centrifugal, so that there may be only slight roughening of the bronchial mucosa, but extensive infiltration of the wall of the bronchus and the surrounding lung (Fig. 522). These are the cases which have been missed in the past. The bronchial lymph nodes are nearly always involved, at autopsy (though not necessarily at operation), and pathological museums are full of specimens labelled "lymphosarcoma with secondary in-

volvement of the bronchial wall," "Hodgkin's disease," "mediastinal
tumor," etc. In the last edition (1922) of Sir John Bland-Sutton's "Tu-
mours, Innocent and Malignant," there is a picture of a typical broncho-
genic carcinoma, but it is entitled "mediastinal lymphosarcoma." If so
great a master as Bland-Sutton could make this mistake, it is no wonder
that his countless readers fell into a similar error. As the disease ex-
tends throughout the lung, the pleura becomes involved, with resulting
pleural effusion, often hemorrhagic in character. The bronchus becomes
obstructed, due usually to contraction of the malignant tissue in the wall
rather than to growth into the lumen; bronchiectasis and lung abscess are
natural sequelae, and this may obscure the main lesion and cause errors
in diagnosis.

In rare cases a *miliary* form may occur, with small nodules scattered
throughout the lung. I have seen two cases which I placed in this category
in which the tumor appeared to have a multicentric origin. One must,
however, admit a two-fold possibility of error: (1) the tumors may be
metastases from a small undiscovered carcinoma in some other organ;
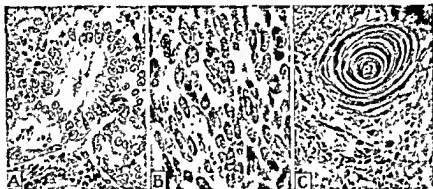
Fig. 523.—Bronchial carcinoma. A, Adenocarcinoma. × 330. B, Anaplastic. × 450. C,
Epidermoid. × 150.

(2) a small primary in a peripheral bronchus may not be detected, and the
nodules may be due to lymphatic spread throughout the lung. Multiple
tumors have been described under a variety of names: alveolar cell tumor
(Neubuerger), carcinoma alveogenica multicentrica (Casilli and White),
etc. Such names suggest an origin from the cells lining the alveoli. The
tumor cells line the alveoli, but do not necessarily arise from the lining.
More readily accepted, on account of its benign character, is the condition
of adenomatosis of the lung described by Richardson, in which small
nodules were scattered through both lungs. These nodules consisted of
glandular spaces lined by mucus-secreting columnar epithelium, which
probably represented a downgrowth of bronchial epithelium into the
alveoli.

Microscopic Appearance.—In many cases microscopic examination
is necessary to make a correct diagnosis. Max Klotz reports two cases
from my department, one of which was thought at autopsy to be pneu-
monia and the other atelectasis, but in both of them microscopic sections
revealed carcinoma. In former days when routine microscopic examina-

tion was not practised, very many cases must have been missed. The tumor may be adenocarcinomatous or epidermoid in type. In the *adeno-carcinoma* (cylindrical cell carcinoma) the glandular arrangement may be evident (Fig. 523A), in which case a diagnosis of carcinoma is self-evident. The tumor cells may creep along inside the alveolar walls and form a new lining within them. Mucin formation may be a marked feature, the cells being distended with clear material. When found in metastases such an appearance is suggestive of a bronchial origin. The cylindrical cells may fail to form glandular acini and may be arranged in masses, an appearance which is medullary in type.

The carcinoma often assumes a *small-cell* or *anaplastic type*. The cells may be round, oval, pleomorphic, or spindle-shaped (Fig. 523B). This is the tumor which in England used to be called oat-cell sarcoma of the mediastinum, the mistake being due partly to the fact that this tumor tends to form a large mass in the mediastinal lymph nodes although the primary lesion in the lung remains small, and partly to the sarcoma-like microscopic picture. Many of these cases have in the past been regarded as lymphosarcoma. The small-cell type has been the commonest in my material both in Toronto and Winnipeg, and the modern recognition of its true character is undoubtedly an important factor in the increased incidence of bronchogenic carcinoma. It has been suggested that this type arises from so-called reserve cells which lie deep to the lining cells of the mucosa, but the great pleomorphism which is characteristic of bronchial neoplasms seems to be a sufficient explanation.

The *squamous-cell type* may be cornifying (Fig. 523C) or noncornifying. In my experience it is less common than the other two, but other observers think otherwise. Thus Gebauer reports 146 cases of which 61 were epidermoid carcinoma, 53 small-cell carcinoma, and 32 adenocarcinoma. It is a question of interpretation. This form is another indication of the growth potentialities of the bronchial epithelium. The metastases may be confined to the lymph nodes, and the tumor is characterized by slower growth, necrosis, cavity formation, and infection.

Spread.—Spread of the tumor is local and distant. Local spread is through the lung and to the bronchial and mediastinal lymph nodes. Spread through the lung may be via the peribronchial and perivascular lymphatics, or the cells may creep or be inhaled along the terminal bronchioles and form a new lining to the alveoli. As a result of lymph spread multiple nodules may be formed throughout the lung and there may be extensive pleural involvement. The tumor may extend to and invade the pericardium and heart, the esophagus, recurrent laryngeal nerve, etc.

Distant spread is extremely common and may involve any organ in the body, but the six common sites for metastases are the lymph nodes and liver, the brain and bones, and the adrenal and kidney. The abdominal, supraclavicular, cervical and even the axillary nodes may be enlarged, again suggesting a diagnosis of lymphosarcoma. The natural history of the disease as shown by distant spread may be so characteristic as to suggest the correct diagnosis. Thus when an adult is found at autopsy to have tumors of the lung, brain and adrenal, a diagnosis may confidently be made of bronchogenic carcinoma. Dosquet has pointed out that whereas in cancer of the lung metastases occur in the brain in 31.4 per cent of

cases and in the adrenals in 21.8 per cent, the figures for other forms of cancer are 0.9 per cent in the brain and 1.9 per cent in the adrenals. In many cases a diagnosis of primary brain tumor is made; only at a later date may pulmonary symptoms make their appearance. The most common cause of secondary carcinoma of the adrenal is primary carcinoma of the lung. In my own experience 50 per cent of adrenal secondary carcinomas have a pulmonary origin, the other 50 per cent including every other site of primary carcinoma.

Relation of Symptoms to Lesions.—The main symptoms may be directly due to bronchial irritation by the tumor; such symptoms are cough (persistent and at first unproductive), blood-stained sputum and dyspnea. As the bronchus becomes occluded, atelectasis develops, as shown by displacement of the heart and limitation of movement on the affected side. Bronchiectasis and lung abscess may be due to the same cause. Fever, which may suggest tuberculosis, is due to infection. Rapidly recurring bloody pleural effusion is due to extension of the tumor to the pleura. Tumor cells may occur in the fluid, but great caution should be exercised in drawing conclusions from the cells of the fluid, as the endothelial cells of the pleura may readily be mistaken for tumor cells.

It not infrequently happens that the principal symptoms are due to metastases in other organs. Thus the patient may present a picture of cerebral tumor, carcinoma of the liver, or anemia due to extensive replacement of the bone marrow rather than carcinoma of the lung.

Apical Carcinoma.—In 1932 Pancoast described a clinical syndrome characterized by pain about the shoulder and down the arm, Horner's syndrome, local destruction of the first two or three ribs, and atrophy of the muscles of the hand. In the roentgen-ray picture there is a small homogeneous shadow at the extreme apex. Pancoast gave it the non-committal name of *superior pulmonary sulcus tumor*. It is now known that in the great majority of these cases the lesion is an apical bronchogenic carcinoma involving the brachial plexus and the sympathetic cervical chain. An important feature of these cases is that symptoms and physical signs of pulmonary disease are nearly always absent. There may be invasion of the vertebral canal by a "dumb-bell tumor," with compression of the spinal cord. Other tumors at the root of the neck may produce a similar syndrome.

Carcinoma of the Trachea.—This rare tumor usually occurs in the lower third of the trachea. It is similar in structure and behavior to bronchial carcinoma, but the metastases are mostly regional. A full review of the literature will be found in Culp's paper.

THE LUNGS

Abscess of the Lung.—A lung abscess may be the result of: (1) aspiration of infected material; (2) breaking down of a pneumonic area; (3) septic embolism. An aseptic embolus may cause an infarct which later becomes infected via the bronchial tree. It may be a complication of bronchiectasis or of bronchial obstruction due to carcinoma.

Aspiration may occur during or after operations on the mouth and upper respiratory tract. The constant danger of inhalation is indicated by the fact that if lipiodol is placed in the nose during sleep, it can be demonstrated in the bronchi next morning. Tonsillectomy, removal of adenoids, and extraction of teeth are of special importance. In Lord's series of 227 cases 1 out of every 3 was due to operations on the upper respiratory tract. Improved technique, however, has materially lessened this danger. Thus 2,000 tonsillectomies done at the Johns Hopkins Hos-

pital were not followed by a single lung abscess. The lodgment in the bronchi of foreign bodies, either metallic or vegetable, may lead to abscess formation. Of these bodies the commonest in the United States is the peanut. Food may pass into the bronchial tree, especially during unconsciousness. Material from new growths and other pathological conditions of the tongue, jaw, etc., may be responsible. In obscure cases the condition of the nasal sinuses should be investigated. Bronchopneumonia, especially when due to staphylococci, may give rise to abscess formation. Such abscesses are likely to be multiple.

The *bacteriology* is mixed in type. The predominant organisms are staphylococci and streptococci. No investigation which does not employ anaerobic methods is of any value, because it is the anaerobes which are

Fig. 524.—Two large chronic abscesses in upper lobe; lobectomy specimen.

responsible for putrefying processes. There is difference of opinion as to the part which Vincent's organisms (spirochetes and fusiform bacilli) play in putrefaction. These organisms are found in the gums, and enormous numbers of spirochetes may be present in Levaditi preparations of the abscess wall, but this is not proof of a causal relationship, for they may be merely secondary invaders of dead tissue.

Morbid Anatomy.—Abscess is more frequent in the right lung, and is as common in the upper as in the lower lobe (Fig. 524). It is usually at the periphery of the lung, and is therefore likely to be in contact with the chest wall, interlobar fissure, diaphragm or mediastinum. The abscess is usually single. At first the lesion is solid, but as liquefaction occurs a cavity develops which contains yellow or greenish pus. The size varies greatly,

but the cavity may occupy an entire lobe. If the abscess is recent the wall is ragged, necrotic and poorly defined; if the cavity is old a fibrous wall may separate it from the rest of the lung. In the inhalation cases the cavity communicates with a bronchus, but this may not be the case in those of different origin. Owing to the close relationship in the pulmonary lobule between the bronchus and blood vessels, thrombosis is frequent, and this leads to extensive necrosis. The lumen of the bronchus is narrowed by inflammatory swelling, so that drainage of the abscess by this route is entirely inadequate. If the obstruction is marked the pulmonary tissue distal to the obstruction undergoes collapse, and a relatively anaerobic area is established favorable to the growth of anaerobic bacteria. The abscess may be putrid or non-putrid, depending on the presence of anaerobic saprophytic bacteria which decompose the dead tissue. If the abscess becomes putrid, the sputum is foul or possesses a peculiar sweetish odor. *Gangrene* of the lung is the result of putrefaction, the tissue becoming greenish in color, liquefied, and having an intolerable fetor.

Chevalier Jackson has called attention to the fact that abscesses due to foreign bodies in the lung form a special class which demands separate consideration. It is in this class that the highest percentage of cures is obtained by bronchoscopic methods, especially when the foreign body is metallic. In these cases, a barrier is built around the infected area. Jackson describes one case in which a metal screw remained in the lung for forty years causing constant trouble, and in which removal of the foreign body by means of the bronchoscope was followed by complete recovery

The *microscopic picture* depends on the acuteness of the process. In an acute case the wall of the abscess is infiltrated with polymorphonuclear leucocytes and macrophages. As the condition becomes more chronic a definite wall of fibrous tissue is formed around the lesion. Occasionally epithelium may grow in from the communicating bronchus and line the abscess cavity. The epithelium may be cuboidal, columnar and squamous in type. The lesion may now resemble a cyst rather than an abscess, and healing has become impossible. In the early stages the surrounding alveoli are filled with a pneumonic exudate, but later this tends to become organized, so that the abscess is surrounded by an area of induration.

The *clinical picture* is characterized by cough and the explosive expectoration of sputum, foul breath and sputum, elastic tissue in the sputum, dulness on percussion, and a characteristic radiographic picture. Any one of these features may be absent.

The *pus* is expectorated suddenly and in large amount, provided the abscess communicates with a bronchus. The *sputum* may be pathognomonic, in which case it is thick, purulent, and of a yellowish or greenish color. On standing in a tall glass it may separate into three layers: an upper frothy layer, a middle cloudy layer, and a lower purulent layer. The odor may be foul or merely disagreeable; in gangrene it becomes overpoweringly offensive. The presence of *elastic tissue* in the sputum indicates destruction of lung tissue, and in the absence of tuberculosis may be taken as proof of abscess formation, especially if it shows an alveolar arrangement. Symptoms of *pleurisy* are common, owing to the peripheral location of the abscess. *Empyema* is due to rupture of the abscess into the pleural cavity. A pleuro-bronchial fistula may develop in

this way. The empyema is often localized, owing to the previous formation of adhesions. *Brain abscess* is a common complication, owing to septic thrombophlebitis in the lung being followed by cerebral embolism. The *X-ray picture* shows a rounded shadow enclosing a rarefied area above and a dense area below, representing respectively air and fluid.

Tuberculosis.—In the past pulmonary tuberculosis has been a purely medical problem, but to an ever greater degree surgery is playing a part in its treatment. There are two great therapeutic problems: (1) how best to achieve rest, (2) how to deal with cavities. The surgeon has an answer to these problems when the internist may be powerless.

Tuberculosis is a chronic inflammatory disease which in man has a strong tendency to heal under favorable conditions. In the lung the initial lesion is a pneumonitis characterized by an accumulation of macrophages (epithelioid cells), the formation of giant cells, and, later, a fibroblastic reaction which may result in healing The early lesions are discrete tubercles, which fuse as the process extends, and the lesion finally becomes caseous. One of two things may now *happen* to the area of caseation: (1) it may be invaded by fibroblasts and converted into scar tissue, a process which is continually in progress in the ordinary fibrocaseous form of the disease; (2) it may undergo liquefaction and discharge into a bronchus, with the formation of a cavity. Every tuberculous cavity therefore communicates with a bronchus. The cavity may be acute (recent) or chronic. The acute cavity is progressive, with a soft wall, irregular outline, and poor drainage. The chronic cavity is stationary, with a thick rigid wall of fibrous tissue, a regular outline, and good drainage; the surrounding parenchyma is also fibrosed. As the disease commences in the upper part of the lung, the principal chronic cavities will be in that region. The infection extends to the surface, so that the affected area becomes adherent to the chest wall, and the pleural cavity is obliterated to a greater or less degree.

A cavity of small or moderate size may become closed, mainly as the result of occlusion of the draining bronchi by obstructive caseous bronchitis or by the formation of a caseous plug (Pagel and Simmonds). The process of healing can be followed in X-ray films. A solid nodule may be formed due to retention and inspissation of the contents with subsequent calcification. Sometimes a radiating scar is produced. Or a bronchiectatic area may develop after replacement of the caseous material by granulation tissue with epithelialization and fibrous shrinking of the cavity.

Larger cavities are permanent, owing to the rigid nature of their walls and the traction of the fibrous bands which radiate into the surrounding parenchyma. Pleural adhesions still further accentuate this state of affairs. If the cavity is well drained and remains clean the condition is compatible with many years of life, but as long as it remains it is a continual menace. Mixed infection may occur, infected material may be aspirated into other parts of the bronchial tree, tubercle bacilli may spread along their favorite route, the lymphatics, into distant parts of the parenchyma, there may be blood vessel invasion with resulting miliary tuberculosis, an artery traversing the cavity may be eroded with severe or fatal hemorrhage, and a communication may be established with the pleural cavity causing a bronchopleural fistula or a pyopneumothorax.

Surgery may attack the problem of the chronic cavity by collapse therapy or by excision. The object of inducing collapse by means of artificial pneumothorax, intrapleural or extrapleural pneumolysis, or thoracoplasty, is not so much to put the lung at rest as to promote closure of the cavity by bringing the walls in contact with one another. If this can be accomplished, retention of secretion ceases and the natural process of healing has a chance to take place. In carefully selected cases it may be possible to excise the affected area. In one case which I studied, the patient, under the care of Dr. R. M. Janes, continued to expectorate tubercle bacilli in spite of radical collapse therapy. Lobectomy was performed, but when the specimen was examined no cavity could be detected until the bronchi were dissected. A small bronchus was then found to lead

Fig. 525.—Small bronchus communicating with cavity filled with thick secretion.

Fig. 526.—Tuberculosis of bronchus × 50.

into a thick-walled cavity the size of a cherry which was filled with thick secretion containing large numbers of tubercle bacilli (Fig. 525).

Tuberculosis of the Bronchi.—Whilst the bronchi must suffer in every case of pulmonary tuberculosis, it sometimes happens that the bronchial tree is the site of the most significant lesions. The early lesion is a submucous infiltration which causes slight elevation of the mucosa (Fig. 526). This may proceed to an *ulcerogranuloma*, which, when it fills the bronchus, causes collapse of the affected part and cuts off the discharge of tubercle bacilli. Healing and *stricture* may occur. The pathologist and the bronchoscopist do not see the same lesions. The ulcerogranuloma is not seen by the pathologist, because it apparently undergoes caseous degeneration shortly before death. The pathologist often sees multiple small erosions which have not been observed by the bronchos-

copist, suggesting that they must be postmortem changes. The attack on the bronchial tree may be more widespread, with the production of *tuberculous bronchitis* and *bronchiectasis*. The morbid anatomy of the latter condition is similar to that of ordinary bronchiectasis, with the addition of tuberculous lesions in the surrounding lung parenchyma. Tuberculous ulcers of the trachea may develop, but these are similar to and associated with those in the bronchus.

Tumors.—The most important tumors of the lung are those arising from the bronchi, namely, carcinoma and adenoma, and these have already been described. Theoretically any of the tissues forming the lungs and bronchi may be the starting point of a tumor, but the only one which needs special mention is hemangioma.

Hemangioma of the lung is a rare condition, but its recognition is important because of the possibility of cure. It consists of a formation of new vascular channels which connect the arterial and venous sides of the pulmonary circulation so that the blood is side-tracked from passing through the capillaries into the alveolar walls It is therefore more of an arterio-venous fistula or shunt than a true hemangio-endothelioma.

The principal features of the condition are well illustrated in the case reported by Hepburn and Dauphinee, which, incidentally, is the first case in which a cure was brought about by pneumonectomy. The patient, a woman 23 years of age, when admitted to the Toronto General Hospital complained of shortness of breath, dizziness, faintness and thick speech, and presented marked cyanosis, clubbing of the fingers and toes, and a polycythemia of over 9 million red cells per cubic millimeter. X-ray examination of the lungs revealed an infiltrating lesion in the right middle and lower lobes. A diagnosis was made of hemangioma of the lung on the evidence suggesting an arterio-venous shunt, and the lung was removed. The lower lobe was occupied by a large angiomatous mass made up of cavernous sinuses, some of which measured 1.5 cm. in diameter. The dyspnea, cyanosis and polycythemia soon disappeared, and a year later the clubbing had also gone.

Cysts.—It is not possible to write a satisfactory account of cysts of the lung, for the pathology is so confused, and there is no correlation between the pathology and the clinical picture. Cysts may be non-parasitic or parasitic (hydatid). The non-parasitic cysts, which alone will be discussed, may be congenital or acquired, although it may be difficult or impossible to be sure to which class a case belongs.

Congenital Cysts.—These cysts are usually found in children and young adults, but they may occur at any age. As a rule they are multiple, and they may be scattered or confluent. They are generally confined to one lobe. There is such great difference of opinion as to their pathogenesis that dogmatic statements are most unwise, but there are three probable origins: (1) congenital bronchiectasis; (2) dilatation of lymphangiomatous spaces; (3) cyst formation in aberrant lung tissue or vestigial structures. Whatever may be the origin of the cyst, its subsequent behavior—and the fate of the patient—depends largely on environmental influences, e. g., communication with air passages, intercurrent infection, and so on. The cyst may contain air or fluid, but a cyst which originally is filled with fluid may discharge its contents into a bronchus and then become dis-

tended with air. Two main types of cavity may be distinguished: (1) those representing dilated bronchioles with concentric muscle fibers, even cartilage, in the wall, and lined by stratified ciliated columnar epithelium; (2) cavities resembling emphysematous blebs. But all kinds of variations and gradations between these types are encountered. A cyst originally containing fluid is likely to be thick-walled and lined by epithelium; a cyst originally containing air is likely to be lacking in these characteristics. A fluid cyst may become infected, and is then filled with pus. An air cyst may communicate with a bronchus by a check-valve mechanism which allows air to enter but not escape. Such a cyst is apt to become ballooned out till it assumes a huge size, displacing the mediastinum and causing extreme dyspnea and cyanosis. This type of lesion may be indistinguishable clinically from pneumothorax, just as a large infected fluid-filled cyst may be confused with lung abscess or empyema. Coogenital cysts may cause symptoms such as cough, dyspnea and cyanosis in early infancy and childhood, or they may not manifest themselves till adult life.

Pneumatocele.—A pneumatocele is a hyperinflated cavity which has originated as a defect in the pulmonary parenchyma. The condition is commoner in children, and often begins as an interstitial pneumonitis with inflammatory narrowing of the bronchus causing a check-valve mechanism. The interalveolar septa in the affected segment are weakened by the inflammation, and as a result of the valvular mechanism the segment becomes blown up with air, so that a cyst is formed which may reach huge dimensions. It has no epithelial lining and contains little or no fluid. In course of time the pneumatocele may subside and disappear; this never happens in congenital cysts of the lung.

Abscess Cyst.—This is an abscess cavity in which suppuration has subsided, and has been followed by an ingrowth of epithelium from the communicating bronchus. The cavity may be lined by cuboidal, columnar or metaplastic squamous epithelium, and the lining may be partial or complete. The lining prevents closure of the cavity. This type of cyst has a much denser fibrous wall than in the case of congenital cysts and pneumatoceles.

Hydatid Cysts.—These cysts due to echinococcus infestation are of extreme rarity in North America. In nearly every instance the infectioa has been acquired in some other part of the world. The cyst presents the usual laminated membrane and is filled with fluid containing the characteristic hooklets.

"Blast" Injury to the Lung.—Exposure to the detonation of high explosive from bombs or shells may produce hemorrhagic lesions of the lung without injury to the chest wall. The lungs show general congestion and extensive deep parenchymal hemorrhages, which may extend to the surface and produce what appear to be subpleural hemorrhages. The alveoli in the hemorrhagic areas are packed with red blood cells, and capillary rupture may be seen. There may be alveolar distension and rupture of alveoli. Hemorrhage may also occur in any of the other viscera.

The explanation of the condition is obscure. It has been suggested that the blast wave set up in the surrounding air may cause sudden distention of the lungs by acting through the respiratory passages, or that the succeeding suction wave may lower the alveolar pressure with consequent

rupture of the alveolar capillaries. It seems more probable that the lesions
are due to impact of the pressure wave on the chest wall. The experimental
work of Zuckerman supports this view. Rabbits exposed to blast suffer
no pulmonary damage if clothed in rubber sponge jackets. If only the side
exposed to the explosion was protected, the lungs suffered little or no
damage, but if the unprotected side was exposed, the lung on that side
suffered much greater damage than that on the protected side.

THE MEDIASTINUM

Acute Mediastinitis.—The mediastinum presents a series of spaces and
fascial planes which extend from the neck into the thorax. It presents two
main spaces, a posterior or retrovisceral and an anterior or vasculovisceral.
The *retrovisceral space* is bounded behind by the prevertebral layer of
cervical fascia, in front by the pharynx, esophagus, and lateral extension
of the retro-esophageal fascia, and laterally by the carotid sheaths. It
extends from the base of the skull to the diaphragm. It is little wonder
that infection spreads so easily from the retropharyngeal and retro-
esophageal regions of the neck into the posterior thoracic mediastinum.
Perforations of the posterior wall of the pharynx or esophagus by foreign
bodies usually involve the retrovisceral space The anterior or *vasculo-
visceral space* contains the pharynx and esophagus behind, the trachea
and thyroid in front, and many lymph nodes and blood vessels, the whole
being surrounded by a cylindrical sheath. It extends from the pharynx
and larynx above to the bifurcation of the trachea below. Into this space
spread infections from the nose, throat and ear, as well as from suppurating
lymph nodes.

The *bacteriology* varies with the source of the infection. In cases of
perforation by a foreign body the tissue spaces are flooded with a mixture
of organisms, including anaerobes and spirochetes. In non-perforative
cases hemolytic streptococci are found most often.

The common sources of infection are perforations of the pharynx and
esophagus by foreign bodies or neoplasm, infections of the mouth and
throat including extraction of teeth, and suppurative cervical lympha-
dentitis. Occasionally infection may spread to the mediastinum from
neighboring structures as in osteomyelitis of the thoracic vertebrae, etc.
The condition is a suppurative one. The pus may discharge through a
perforation into a bronchus or the pleural cavity. Although there is defi-
nite resistance to the spread of the infection, there is no encapsulation by
means of an inflammatory envelope, and fulminating cases may cause death
in two or three days. On the other hand recovery may follow operation even
in advanced cases. The principal clinical features are dyspnea, dysphagia,
cyanosis, fever, and marked X-ray widening of the mediastinum.

Mediastinal Tumors.—The mediastinum is a highly complex structure
containing a great variety of tissues. It is natural that a great mixture of
tumors should have been reported. They may, however, be divided into
two great groups: tumors of the anterior mediastinum and tumors of the
posterior mediastinum. The chief tumors of the anterior mediastinum are
teratomas and lymphomas in about equal numbers; those in the posterior
mediastinum are for the most part neurogenic in origin.

Teratomas.—These tumors are also known as dermoids, on account

of the dermal structures which they contain, but Harrington, pointing out that careful examination may reveal mesodermal and entodermal as well as ectodermal structures, suggests the term *teratoid tumors*. Their precise origin has never been settled, although all sorts of suggestions, fantastic and otherwise, have been offered. Origin from a segregated blastomere (a true teratoma) or from developmental misfits in the formation of the mediastinum are the two most reasonable views. The tumors are almost confined to the anterior mediastinum, although rare examples may occur in the posterior mediastinum. They may project into either pleural cavity. The tumor may be solid or cystic. The lining of the cyst may be columnar or squamous stratified epithelium, and amongst the possible contents are hair and sebaceous material, sebaceous, sweat, mucous and salivary glands, cartilage, bone, nerves, etc. Although the lesion is benign to begin with, it may develop into adenocarcinoma or epidermoid carcinoma, a possibility which indicates the necessity of complete removal.

The tumor usually manifests itself in the early adult and middle age period and is commoner in women. Amongst the more frequent symptoms are dyspnea, pain and cough. X-rays show a shadow in the anterior mediastinum. The subjective symptoms are characteristically intermittent, and progression is gradual.

Lymphangiomas or Cystic Hygromas.—These are amongst the rarest forms of mediastinal cysts. The structure is similar to that of the cystic hygroma of the neck, *i. e.*, large, thin-walled, multiloculated structures containing watery fluid and lined by endothelium. It has been suggested that they arise from a portion of the anlage for lymphatic formation in the neck being drawn down by the pericardium in its descent, or from the pericardium as a result of defects in its development (Lambert).

Lymphomas.—Tumors of the anterior mediastinum may arise from the lymph nodes in that region. The various malignant lymph-node tumors, lymphosarcoma, reticulum-cell sarcoma and Hodgkin's disease, have already been described in connection with diseases of the lymph nodes, and need not be recapitulated here. There may be no generalized lymph-node involvement. The high degree of radiosensitivity as indicated by shrinkage of the X-ray shadow is a valuable diagnostic feature in distinguishing them from operable tumors. In my student days mediastinal lymphosarcomas appeared to be common, owing to bronchogenic carcinomas with massive lymph-node involvement being mistaken for these tumors.

Neurogenic Tumors.—Tumors very often arise from the posterior mediastinum or from the chest wall. Many names have been applied to these neoplasms, but it may be said in general that they may originate from spinal nerves, being benign (neurofibroma) or malignant (neurogenic sarcoma), or from sympathetic structures (ganglioneuroma). The common tumor is the neurofibroma, resembling an ordinary fibroma in gross and microscopic appearance except that the fasciculi of fibers have a characteristically interlacing arrangement. If the tumor is left alone it tends to develop into a neurogenic sarcoma. It is for this reason that most of the surgical cases reported by Harrington and others have been benign. whereas those observed at autopsy have usually been malignant. The benign tumors are remarkable for the size they may attain without pro-

ducing symptoms. In the malignant form pain is a marked feature due to invasion. The tumor may grow through the intervertebral foramen into the spinal canal, forming the so-called "dumbbell tumor." The ganglioneuroma, which is a tumor of childhood, contains not only nonmedullated nerve fibers but sympathetic ganglion cells. It is entirely benign. The detailed microscopic features of these various tumors are considered on page 661.

Miscellaneous Tumors.—Lipoma is a rare tumor of the mediastinum. It is benign and of slow growth, so that it may attain a great size before producing symptoms. It may remain intrathoracic, or may grow up into the neck or out between the ribs. Removal is not difficult, but the patient is very likely to die. During the slow growth of the tumor the heart and lungs have gradually become accommodated to strains and pressures which are suddenly released when the tumor is removed, often with fatal results.

Thymoma is the non-committal name given to tumors of the thymus gland. The neoplasm may be benign or malignant. The benign lesions tend to reproduce the various elements of the normal thymus which is the chief reason for using the name thymoma. It may attain a great size, Andrus and Foot reporting one (successfully removed) weighing 2235 grams. The malignant thymoma may be sarcomatous or carcinomatous in type. The former resembles lymphosarcoma or reticulum cell sarcoma, while the latter resembles epidermoid carcinoma, being composed of innumerable thymic corpuscles in all stages of development and degeneration thus giving a 'pearly' appearance. For a discussion of these complex tumors Foot's paper should be consulted.

Xanthoma is a rare tumor composed of large "foamy" cells distended with doubly refractive lipoid, probably cholesterol ester. The characteristic highly vacuolated cells are illustrated in Phillips' paper. The tumor, which is benign, is firm, encapsulated, and the cut surface is of a peculiar yellowish color from which the name xanthoma is derived. The color is due to the lipoid. The origin is from the costovertebral groove.

PLEURA AND PLEURAL CAVITY

Empyema (Acute Suppurative Pleurisy).—*Etiology.*—Purulent infection of the pleural cavity may be due to bacteria introduced from without, or to spread from neighboring organs. Introduction from without is of special importance in the perforating wounds of military surgery; here the bacteriology may be very mixed. In civil practice the vast majority of cases are due to spread of infection from the lung, but infection may come from the heart, pericardium, mediastinum or chest wall; it may also pass through the diaphragm from a subphrenic abscess.

The three common organisms are pneumococcus, streptococcus, and staphylococcus in that order. Pneumococcal empyema is by far the most frequent. This is particularly true of children. In Lanman and Dimmler's series of acute empyemas in children 80 per cent were due to pneumococcus; 10 per cent each to streptococcus and staphylococcus. Tuberculous empyema forms a separate group.

In streptococcal and staphylococcal empyemas infection of the pleural cavity is usually due to rupture of a subpleural lung abscess into that cavity (Fig. 527), but in some streptococcal cases there appears to be diffuse infection of the pleura through the interstitial tissue of the lung, for no subpleural abscess may be demonstrable. The presence of a few bacteria is not sufficient to produce an empyema, any more than a few bacteria in the peritoneal cavity can cause peritonitis. A heavy infection is necessary. The American Empyema Commission showed that in the streptococcal cases complicating the last influenza pandemic this heavy

infection was due in nearly every case to the bursting of a subpleural abscess, although these abscesses were frequently small and at times difficult of detection. The explanation of empyema in lobar pneumonia is by no means clear, for as a rule no abscess can be found, and at the time the empyema develops the lung is coated with a protective layer of fibrin.

The distinction between pneumococcal and streptococcal empyema is of profound clinical significance. Pneumococcal empyema follows rather than accompanies lobar pneumonia. The patient is recovering from his pneumonia by the time the empyema has developed; he is no longer acutely ill, the pleural cavity is occupied by a sponge-like mass of fibrin, and there is no collapse of the lung when the chest is opened.

Fig. 527.—Subpleural abscess at base of lung associated with empyema

In empyema complicating streptococcal pneumonia the state of affairs is quite different. Here the exudate may commence to form at the very beginning of the illness. Moreover, it is sero-fibrinous rather than purulent at first, and it may take from two to three weeks to become frankly purulent, although this is by no means always the case. The fluid exudate accumulates with great rapidity, so that the chest may be full of fluid while the patient is still at the height of his pneumonia. He presents a picture of anoxemia characterized by acute air-hunger and intense cyanosis due to the pneumonia rather than to the empyema. In the 1918 epidemic of influenza the pleural cavity was at first opened and drained as soon as the effusion was detected, with what disastrous results may be read in the pages of the Empyema Commission's Report. Not only did the lung on the side that was opened collapse completely, due to the pneumothorax, but, owing to the mobility of the normal mediastinum, the

opposite lung, itself often pneumonic, was also compressed. Moreover, the patient in this condition has a low vital capacity, and even a small pneumothorax may be fatal under these circumstances. It is for these reasons that in acute streptococcal empyema only aspiration or closed drainage is permissible, whereas in pneumococcal empyema either open or closed drainage may be employed. The result was what might have been anticipated. When, however, the waiting policy was introduced, and the chest was not opened until the pneumonia had subsided, it was found that the formation of adhesions had converted the mediastinum into a rigid partition, so that the thorax no longer behaved as a single chamber but as two separate cavities. The ad-
hesions, moreover, prevent the lung from collapsing still further when pneu-
mothorax is induced. It might be thought that the presence of a large pleural exudate full of virulent strep-
tococci was a source of great danger, but patients can carry around such an exudate for weeks or even months with-
out serious hurt. The real danger in these cases is from the pneumonia.

Morbid Anatomy.—The *pleura* is covered by a thick and shaggy exu-
date, often laid down in great masses and waves, covering not only the visceral but also the parietal pleura. As time goes on the pleural exudate becomes invaded by fibroblasts and a most extensive fibrosis takes place. In this way the surface of the lung be-
comes covered by a great layer of fibrous tissue which in one of our cases reached 1 inch in thickness. Such a layer must necessarily exert a profound influence on the subsequent fate of the collapsed lung. The parietal pleura is covered by a similar layer which will offer great resistance to the exploring needle. This general fibrosis also affects the mediastinum and imparts to that

Fig. 528.—Empyema with collapse of the lung showing the thick pleural deposit.

partition a rigidity which it does not normally possess. The experimental work of Graham and Bell has shown that a pneumothorax in a normal animal produces a considerable amount of collapse of the opposite lung, owing to the mobility of the mediastinal partition. Such an effect is no longer seen when that partition is stiffened by fibrosis and adhesions. This is one of the reasons why in the influenzal cases the late operation was so infinitely better than the early one.

The empyema may be *encapsulated* or localized rather than diffuse. This is caused by adhesions either to the chest wall or between the lobes of the lung. The common form is encapsulation over the convexity of the

lung, but in addition there are interlobar, intrapulmonary (between base of lung and diaphragm), and paramediastinal (on mesial or mediastinal aspect of the pleura).

The *lung* is in a condition of collapse, in extreme cases being flattened against the mediastinum and posterior chest wall and so covered by exudate as to be almost indistinguishable (Fig. 528). In time the exudate becomes organized into fibrous tissue which may bind the lung down permanently.

The *pus* varies with the bacteriology. In pneumococcal cases it is thick, yellow, and creamy, in a word intensely purulent. In streptococcal infections it is at first thin and watery, and later more serous than purulent, containing great numbers of organisms. When the infection is due to rupture of the esophagus the exudate is thin and of a greyish-black color.

Tuberculous Empyema.—This is secondary to a lesion in the lung. It formed 2 per cent of Wilensky's cases of empyema. The commonest exciting cause of tuberculous empyema is artificial pneumothorax. In some cases the empyema seems to be due to a secondary invader, which dies out later and leaves the tubercle bacillus in possession. The pus has no constant characters. It tends to be thin and watery, with masses of caseous material, but I have seen more than one example where the pus was thick and creamy. The fluid may be blood-stained.

Chronic Empyema.—After operation the empyema cavity may refuse to close and continue to discharge pus. It becomes a chronic empyema. For this there may be a number of reasons. A broncho-pleural fistula, a permanent communication between the bronchial tree and pleural cavity, may keep up the infection. The lung may be unable to expand and fill the pleural cavity owing to the thick layer first of fibrin and later of fibrous tissue which covers it. Osteomyelitis of a rib may act as a continual source of fresh infection. A localized atelectasis caused by bronchial obstruction due to thick secretion may be responsible for a persistent pocket of pus; if the obstruction is removed by means of the bronchoscope the empyema may soon clear up. The most important single cause of chronic empyema is the improper handling of the acute infection.

Broncho-pleural Fistula.—A connection between the pleural cavity and the bronchial tree may be due to: (1) pulmonary tuberculosis, frequently as a complication of artificial pneumothorax; (2) a neglected empyema; (3) drainage of a lung abscess; (4) trauma. Of these the first is much the commonest and most important. The fistula may be transient, intermittent, or continuous. Its size varies widely. It may be microscopic, too small to be observed at autopsy, and undetectable during life without gas analysis of the air in the pleural cavity. In only about one-third of the cases can a gross fistula be detected. Gas analysis reveals how common the condition really is. In Woodruff's paper will be found a remarkable description of gas analysis employed by John Davy in 1823 in an autopsy case in which atmospheric air was demonstrated in the pleural cavity. On the other hand the fistula may be a large opening between a tuberculous cavity and the pleura. The fistula is commonly caused by artificial pneumothorax, especially if the collapse is incomplete, or it may be the cause of a pneumothorax. In tuberculosis it is the chief cause of a change

from a clear pleural effusion to a purulent one. The infection is commonly a mixed one.

The principal effects of the establishment of a broncho-pleural fistula are a change in the intrapleural pressure, infection of the pleural cavity with tubercle bacilli or pyogenic cocci, and the aspiration of pleural exudate into a bronchus. As a result of this aspiration there may be expectoration of pleural fluid or of *methylene blue injected into the pleural cavity*. In general terms it may be said that any change in the nature of the symptoms suggests the formation of a broncho-pleural fistula, but in many cases it is not possible to make a clinical diagnosis.

Tumors.—These may be primary or secondary. The former are rare, the latter very common. The primary tumors, with which alone the surgeon is concerned, are of two entirely different types, localized and diffuse.

Localized Tumors.—These tumors arise from the subpleural tissues, not from the lining cells. They may grow from the parietal or visceral
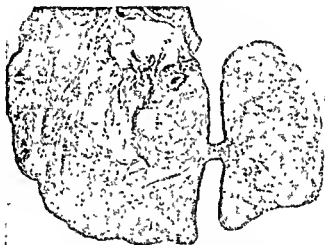
Fig. 529.—*Unusually large pedunculated fibroma of pleura*

pleura. The *parietal tumors* present a great variety of forms, as they may originate from any of the structures underlying the pleura, e. g., the fascia of the intercostal muscles, the nerve sheaths, the subpleural fat, etc. They are malignant, and are described in the literature as round- or spindle-cell sarcoma, angiosarcoma, liposarcoma, neurosarcoma, etc. They invade the chest wall, and metastasize to the mediastinal lymph nodes and even to the abdominal viscera.

The *visceral tumors* take the form of fibromas (Fig. 529), lipomas, chondromas, etc. They are not invasive, and are found by accident at autopsy. Of much greater interest are the so-called *giant sarcomas*. Although the microscopic picture is that of a sarcoma, they are not invasive nor do they metastasize. They grow slowly and attain an enormous size, filling the thoracic cavity and displacing the heart to a fatal degree. The tumor is surrounded by a connective tissue capsule and is often pedunculated, so that before it becomes too large it may be removed with safety. *Microscopically* it presents a picture of fibrosarcoma; tumor giant

cells may be present. Several examples are illustrated in the excellent paper by Klemperer and Rabin.

Diffuse Endothelioma.—This is a tumor of the cells covering the membrane. The lining of the pleuro-pericardial cavity develops from the celomic epithelium which is formed by splitting of the mesoderm and is mesothelial in nature, with the power of developing tumors which may present both epithelial and mesenchymal characteristics. These mesotheliomas are remarkably diffuse and may extend over a wide area, sometimes enveloping the entire lung with a thick layer of tumor. There is usually a pleural effusion, which is hemorrhagic in the later stages. *Microscopically* the tumor is composed of large, polygonal, epithelial-like cells, separated into alveolar groups by connective tissue.

Cysts.—Primary serous cysts of the parietal pleura are of rare occurrence. They gradually increase in size, and present the characteristics of a benign tumor. They contain serous fluid, and as a rule are lined by endothelium, although in Tudor Edwards' case the wall was composed only of fibrous tissue. During development diverticula of the pleural cavity are known to occur, and it seems probable that these may form the starting point of the cyst. In some cases a similar origin from the pericardium is possible.

TUMORS OF CHEST WALL

Tumors of the chest wall may arise from the soft tissues or from the bone. The usual skin tumors are taken for granted. The soft-part tumors may be innocent or malignant. The chief representative of the former group is lipoma; sarcoma, of the latter group. *Lipoma* is noteworthy chiefly because of the great size which it may attain. If it arises in the deeper part of the intercostal space, it may grow outwards and inwards, assuming a dumb-bell appearance like that of the neuroma of spinal nerves. *Fibrosarcoma* is probably the commonest of the malignant tumors, although from the microscopic description of some of these cases they appear to belong to the neurogenic group. Their tendency to recurrence even after wide removal and their radioresistance support this view. *Lymphangioma* (cystic hygroma) may form a large, soft, fluctuant tumor on the chest wall of children.

Tumors of the ribs may be primary or secondary. The former are rare, the latter common. *Chondroma or chondrosarcoma* is the chief, primary tumor. It may be difficult or impossible to distinguish between the benign and malignant forms by microscopic examination. Rapidity of growth is more valuable, together with X-ray evidence of invasion. A chondroma may remain benign for many years and then become malignant, an indication of the necessity to remove benign lesions. The tumor may show calcification or ossification. Destructive tumors of the ribs are giant-cell tumor and multiple myeloma. Of rare occurrence are osteogenic sarcoma and Ewing's tumor.

SURGICAL PATHOLOGY OF THE HEART

The heart is the last of the great organs of the body to be taken into the domain of the surgeon. It is true that wounds of the myocardium have been repaired with success for some time, but the most striking recent

advances have been in the treatment of congenital heart disease and in some forms of pericarditis.

CONGENITAL HEART DISEASE

It is of interest to note that in a monograph devoted to the surgery of the heart published in 1941 the statement occurs: "Little has been achieved as yet in the treatment of developmental conditions." Yet now surgery has much to offer in the treatment of three major congenital lesions, namely, patent ductus arteriosus, pulmonary stenosis, and coarctation of the aorta. Of the endless varieties of congenital anomalies only those will be considered in which at least some alleviation can at present be offered by surgical intervention. It seems probable that the surgical field will be still further widened in the future.

The key to most of the congenital defects lies in variations in the formation of the septum which divides the heart into a right and left side. The primitive heart consists of three chambers, auricle, ventricle, and aortic bulb. Separate septa are formed which divide these chambers into right and left sides, and subsequently fuse. If anything goes wrong with this fusion, congenital defects will result.

The most fundamental developmental defect is a deviation of the septum to the right, so that the pulmonary artery becomes narrowed, while the aorta is widened (dextroposition of the aorta). The aorta consequently partially overrides the right ventricle, and the aortic septum is unable to meet the ventricular septum, so that there is a high defect in the ventricular septum. Even should this not occur, the heightened pressure in the right ventricle resulting from the pulmonary stenosis will cause the blood to flow from the right into the left ventricle, thus tending to interfere with the normal closure of the interventricular septum. The same is true of closure of the ductus arteriosus, which connects the pulmonary artery with the aorta in intrauterine life. The combination of pulmonary stenosis, displacement of the aorta to the right, enlargement of the right ventricle and a defect in the interventricular septum is known as the *tetralogy of Fallot*.

The various congenital cardiac anomalies can be divided into two great groups: those in which there is an arterio-venous shunt with intermingling of the blood in the systemic and pulmonary circulations, and those in which no such communication exists. Cyanosis, which is so important a feature of congenital heart disease, is only present when blood flows from the right side of the heart into the left (venous-arterial shunt). This may occur if the septal defect is large, if the pressure on the right side is raised by pulmonary stenosis or failure of the left ventricle, or if the aorta arises partly from the right ventricle. The flow may originally be from left to right, but when left-sided failure sets in the direction of flow may be reversed. It may be noted that even the most extreme degree of cyanosis is not associated with edema, a highly characteristic feature.

Pulmonary Stenosis.—This is the most important congenital lesion of the heart. The stenosis varies greatly in degree, and there may be complete atresia. In the latter case it is evident that no blood will reach the lungs unless the ductus arteriosus remains patent. Early closure of the ductus is therefore incompatible with life unless, as occasionally happens,

the bronchial arteries dilate sufficiently to establish an adequate collateral circulation. In those patients who survive for many years there is a balance between the degree of stenosis of the pulmonary opening and the patency of the ductus. The valve is bicuspid, and the leaflets are thick and fleshy, being fused to form a kind of diaphragm in the center of which there is a small opening. Sometimes there may be complete atresia. The pulmonary conus and the main pulmonary artery are narrow and hypoplastic, whilst the aorta is wide and thick-walled, and rides above the septal defect which is frequently present in the upper part of the interventricular septum, so that it receives blood from the right as well as the
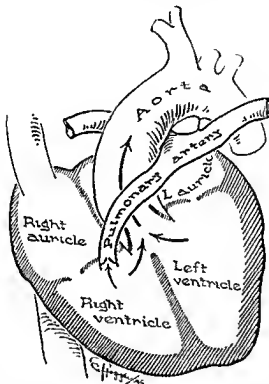
Fig 530.—Tetralogy of Fallot, showing pulmonary stenosis, wide aorta, hypertrophied right ventricle, and defect in interventricular septum.

left ventricle. As already pointed out, the combination of pulmonary stenosis, dextroposition of the aorta, enlargement of the right ventricle and a defect in the interventricular septum constitutes the tetralogy of Fallot. (Fig. 530).

The diagnosis of pulmonary stenosis can be made with a high degree of accuracy. Owing to the small amount of blood reaching the lungs there is likely to be a marked degree of cyanosis; the patient is the classical "blue baby." Of course if the ductus remains widely patent this cyanosis will not be present, because a sufficient amount of blood is poured into the pulmonary artery from the aorta. A compensatory polycythemia will accompany the cyanosis. The oxygen content of the peripheral blood is

low. Dyspnea may be severe. X-ray studies reveal the small size of the pulmonary artery, the fulness of the normal pulmonary conus being replaced by a concave shadow.

At first sight it would appear that nothing could be farther from the field of operative surgery than the state of affairs outlined above. Nevertheless Blalock and Taussig have devised an operation which has succeeded in restoring the circulation to normal and the child to health. The principle is to bypass the obstruction by constructing an artificial patent ductus arteriosus, so that an adequate supply of blood is poured into the pulmonary circulation. One of the main branches of the aorta, either the innominate or the left subclavian artery, is anastomosed to the right or left pulmonary artery just distal to the bifurcation of the main artery in such a way that the blood flows to both lungs. This in many cases at once relieves the cyanosis, which is due in great part to direct shunting of the venous blood into the systemic circulation by way of the opening in the interventricular septum. The polycythemia tends to be replaced by a normal red cell count. The dyspnea is a thing of the past, and the child is now able to develop along normal lines. The most suitable cases are those presenting the tetralogy of Fallot with a small or closed ductus. The best age for operation appears to be between four and six years, but if the stenosis is extreme and closure of the ductus arteriosus renders the malformation incompatible with life, the operation must be performed in early infancy.

Patent Ductus Arteriosus.—The ductus arteriosus, which in intrauterine life pours the blood from the right heart into the aorta, thus bypassing the lungs, arises at the bifurcation of the pulmonary artery and ends in the aorta beyond the commencement of the left subclavian artery. In the full term fetus it is 1.5 cm. long and approximates in diameter the descending aorta. Functional closure of the ductus occurs within a few minutes of delivery due to contraction of the abundant smooth muscle in the wall. Subsequent obliteration is the result of subendothelial fibrosis, and becomes complete in the course of a month.

When the ductus remains patent, a condition which is twice as common in females as in males, the blood flows from the aorta into the pulmonary artery, owing to the higher pressure in the aorta. In uncomplicated cases, therefore, there is no cyanosis. There may, however, be a temporary reversal of flow due to prolonged crying, violent physical exertion, or terminal heart failure, with resulting cyanosis. If the ductus is acting as a compensatory mechanism to other congenital cardiac anomalies, cyanosis may be present even under resting conditions. In some cases as much as half the blood from the left ventricle may pass into the pulmonary artery. As a result of this there may be marked retardation of growth. There may be a characteristic continuous rumbling murmur, widespread, but loudest over the pulmonary area (Gibson murmur). If the leak is large the murmur may be accompanied by a systolic thrill. A tube can be passed into a vein in the arm, and onwards into the jugular vein, right auricle and ventricle, finally entering the pulmonary artery. By this means the pressure effect of the flow of arterial blood into the pulmonary artery can be demonstrated and the increased oxygen content of the blood can be determined, so that the diagnosis can be confirmed with absolute certainty.

The condition is compatible with a long and active life, but in the great majority of cases life expectation is considerably shortened, although there may be no serious disability for many years. About 70 per cent of persons with a patent ductus who live to three years of age die before the age of forty from causes mostly related to the heart (Trent). The great danger, which always hangs as a threat over the patient, is the development of Streptococcus viridans endarteritis, a condition analogous to subacute bacterial endocarditis. This complication occurs in about 25 per cent of cases. The vegetations are formed at the pulmonary end of the ductus, and they may spread into the pulmonary artery.

It was in 1938 that Robert Gross first ligated a patent ductus, and since that time this operation, now superseded where possible by complete division, has been performed in large numbers of cases with a negligible mortality. Not only does the operation prevent a possible Streptococcus viridans infection, but it usually results in the cure of an already established endarteritis. This remarkable result has not been satisfactorily explained. It may be related to the fact that the blood in contact with the lesion is now venous and very low in oxygen concentration. It is of course common knowledge that endocarditis is comparatively rare on the right side of the heart. Furthermore, if there is evidence of preoperative systemic embolism, operation seldom or never results in cure.

Coarctation of the Aorta.—In this condition the aorta is narrowed at a point between the origin of the subclavian artery and the opening of the ductus arteriosus. In the extreme cases the lumen may be only 2 or 3 mm. in diameter or there may be complete atresia. The coarctation probably originates at or shortly after birth during the process of involution of the ductus arteriosus by the extension of the obliterative process into the wall of the aorta.

In severe cases the diagnosis can be made with great accuracy. The two most distinctive physical signs are a relative weakness and delay in the pulse of the lower limbs, and the presence of characteristic anastomotic vessels. Owing to the obstruction the blood pressure in the upper portion of the body, including the arms, is raised. This is one of the causes of hypertension in a young person. The blood reaches the lower part of the body through collateral vessels which become greatly dilated. The principal of these are the subscapular arteries which anastomose with the intercostals and the internal mammary arteries which anastomose with the epigastrics. By these routes the blood reaches the aorta below the constriction. Characteristic scalloping of the lower margins of the ribs due to erosion by the dilated intercostal arteries and also grooving of the ribs by the enlarged internal mammary artery can be seen in the X-ray film.

Mild forms of the condition are compatible with a comparatively long life, but the average span of life is greatly diminished. As a rule there are few symptoms in childhood. The hazards which must be borne in mind are: (1) severe hypertension in the upper part of the body, with resulting cardiac failure, cerebral hemorrhage, etc.; (2) Streptococcus viridans endarteritis at the site of coarctation, analogous to the similar infection which so frequently complicates patent ductus arteriosus; (3) aneurism formation immediately above or below the constriction owing to faulty

development of the aortic wall; (4) development of a dissecting aneurism; (5) rupture of the aorta.

Gross and Hufnagel have shown that it is possible to divide the descending aorta in the dog and suture the divided ends without ill effects, although in the occasional case there was paralysis of the hind legs due to ischemic necrosis of the spinal cord. In coarctation the problem is simpler on account of the abundant collateral circulation, and Crafoord and Nylin as well as Gross have successfully treated a number of cases by resection of the stenosed segment and end to end anastomosis. The clamps on the aorta must be released gradually, otherwise the sudden release of pressure may lead to fatal fibrillation of the left ventricle.

VALVULAR DISEASE

A considerable amount of experimental work has been done with the object of devising some method of relieving valvular conditions such as mitral stenosis. A few attempts have been made on the human subject. It cannot be said, however, that any operation either inside or outside the heart (such as slitting the pericardium) holds out any promise at the present time.

CORONARY ARTERY OCCLUSION

The significant result of coronary artery occlusion, commonly caused by thrombosis, is infarction of the myocardium due to ischemia. Nothing can be done about this lesion, once produced, for the heart muscle is dead in the infarcted area, and the surgeon cannot provide new muscle. In these cases there is always the danger of the formation of further infarcts, because the coronary atheroma which is the basic lesion is likely to be progressive. Nature's method of warding off this catastrophe is by establishing a remarkably abundant collateral circulation between the right and left coronary arteries, as can be demonstrated by injecting these vessels.

Various attempts have been made by Beck and others to produce artificially an increased collateral circulation, and thus prevent the development of further ischemia. This has been done: (1) by establishing extracoronary communications by attaching to the anterior wall of the heart such structures as an omental flap or a flap of muscle from the chest wall; (2) by establishing intercoronary communications by means of inflammation on the surface of the heart produced by powdered asbestos. Animal experiments have been encouraging, but this cannot so far be said of the clinical results in man.

THE PERICARDIUM

Purulent Pericarditis.—This acute form of inflammation is caused by one of the pyogenic cocci (staphylococcus, streptococcus, pneumococcus), the infection usually extending from one of the many structures with which the pericardium is in contact. The sac is filled with pus. As the condition is acute, the pericardium has no time to stretch. There is therefore great danger of acute compression of the heart with fatal results unless the condition is relieved by operation. Spontaneous recovery sometimes occurs, leaving marked thickening of the pericardium and adhesions between its two layers.

Tuberculous Pericarditis.—Tuberculous pericarditis is not uncommon in early life. Graham, Singer and Ballon say that it is the commonest cause of pericarditis in the aged. It is usually due to extension of infection from the lymph nodes in the anterior mediastinum. The process passes through three stages: (1) an acute fibrinous stage; (2) a stage of effusion; (3) a stage in which the effusion disappears, and both pericardium and epicardium become converted into dense scar tissue which may be as much as 1 cm. in thickness. In this fibrous tissue it may be possible to find persisting evidence of tuberculosis, or all trace of the original disease may be lost. Tuberculosis is the principal cause of chronic constrictive pericarditis.

Chronic Constrictive Pericarditis.—One of the most remarkable conditions to come under the notice of the surgeon is compression of the heart due to a layer of dense tough fibrous tissue which envelops the organ. The thickened pericardium prevents relaxation of the ventricles in diastole and contraction in systole. The compressed heart is small and quiet, because it cannot undergo dilatation or hypertrophy. There may be no trace of pulsation over the precordium. It receives too little blood, and therefore undergoes disuse atrophy, which may account for the long delay in recovery after operation. The compression force may be as high as 40 to 45 cm. of water. What Beck calls the triad of chronic cardiac compression are (1) a small quiet heart; (2) high venous pressure; (3) ascites and enlargement of the liver. The liver and spleen may be coated with an exudate at first fibrinous and later fibrous, the so-called sugar-icing, apparently the result of the long-continued ascites. The peritoneum may show similar thickening. Acute compression is always due to fluid. Chronic compression may be caused by fluid, scar tissue or tumor.

It used to be thought that widespread adhesions, the adherent pericardium, were responsible for dilatation and hypertrophy, but this idea has had to be given up. These changes are due not to adhesions but to concomitant valvular and myocardial lesions. Hosler and Williams stitched the heart to the diaphragm, but these experimental adhesions failed to produce dilatation or hypertrophy.

There is still great uncertainty as to the cause of the dense envelope responsible for the compression. Rheumatic pericarditis apparently never causes constriction. In the non-constrictive cases the picture is one of inflammation followed by healing, without extensive destruction of tissue. The scar is thin, the fibers are firm and slender, blood vessels are numerous, and there are chronic inflammatory cells.

In constrictive pericarditis the envelope is thicker, denser, tougher, and may present large cavities containing inspissated caseous débris. The collagen fibers are huge, the tissue is hyalinized, calcification is common; it is a picture of devastating inflammation with great tissue destruction. Beck produced the condition experimentally by irrigating the pericardial cavity with Dakin's solution. It seems probable that most cases are tuberculous, although complete healing may have occurred. Beck believes that septic pericarditis is the chief cause. Removal of the constricting tissue may result in complete cure. It is true that post-operative adhesions will develop, but these are of the ordinary inflammatory type and do not interfere with cardiac function.

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CHAPTER XXXIV

MIDDLE EAR INFLAMMATION

Whilst diseases of the ear come into the domain of the specialist rather than of the general surgeon, inflammation of the middle ear provides a notable exception because at any moment, at any stage of the disease, the inflammation may spread to neighboring vital organs with far-reaching consequences and disastrous effects. The sword of Damocles hangs suspended over the patient by a very thin thread.

Etiology.—The bacteria which are responsible for the inflammation may reach the middle ear: (1) from the external meatus, (2) from the naso-pharynx via the Eustachian tube, or (3) through the blood stream.

The first variety may follow rupture of the tympanic membrane from forcible syringing, the unskilled use of instruments, and fracture of the skull. Any form of external otitis may spread to the middle ear, and foreign bodies and impacted wax may act as exciting causes.

The second variety is predisposed to by any chronic pathological condition of the nose or naso-pharynx of which the most important are adenoids in children and chronic catarrh. Acute infections of the throat such as diphtheria may travel upwards along the Eustachian tube. Clumsy syringing of the nose may force fluids along the same route.

The third variety in which infection is carried by the blood stream occurs in the acute exanthemata, of which scarlet fever, measles, and influenza furnish the most important examples. In these conditions it may be difficult to exclude upward spread from the usually inflamed throat. Tuberculosis of the middle ear is also due to blood spread from some primary focus.

The *bacterial flora* is varied. In acute infections, such as those which complicate scarlet fever and influenza, Streptococcus pyogenes is usually found. A peculiarly viscid or slimy discharge is due to infection with Streptococcus mucosus, an organism which, in spite of its name, is more closely allied to pneumococci than to the streptococci. In exceptional cases the diphtheria bacillus may be present. Those cases due to spread of infection from the throat will usually show the pneumococcus or the streptococcus. When the inflammation has become chronic with discharge through a perforation in the membrane, the staphylococcus, either aureus or albus, replaces the pneumococci and streptococci. In these chronic cases a green or blue color in the pus indicates the presence of Bacillus pyocyaneus. The tubercle bacillus may be found in the discharge. Speaking generally it may be said that in the acute cases the infection is likely to be pure, in the chronic cases it will most probably be mixed. Pneumococcal infections are most prone to set up mastoid and extra-aural abscesses.

Middle ear inflammation has been subdivided and classified in various ways, but for our present purpose it will be sufficient to recognize two main forms, the catarrhal and the purulent.

Catarrhal otitis media is characterized by swelling and hyperemia of the mucosa lining the tympanum accompanied by a serous or mucoid discharge and not leading to perforation of the tympanic membrane. The inflammatory swelling of the mucosa never reaches an extreme degree, and may entirely subside but inflammation in the middle ear differs from that affecting the mucous membranes of other organs in that there is a great tendency to the formation of very persistent masses of granulation tissue with permanent thickening and adhesions between the tympanic membrane, the ossicles, and the walls of the tympanic cavity, a catarrhal adhesive process of more interest to the otologist than to the general surgeon. The secretion is either quite clear and serous, or viscid and sticky. The inflammation is not severe enough to destroy a portion of the tympanic membrane and thus produce a perforation.

Purulent otitis media differs from the foregoing in the acuteness of the process, in the character of the secretion, and in the involvement of the membrana tympani. The entire mucosa lining the tympanic cavity becomes swollen and intensely hyperemic, and in the most severe cases may display petechial hemorrhages. The submucous connective tissue is infiltrated with inflammatory serum and cells, and in places the surface epithelium may be cast off into the exudate in the cavity. The tympanic membrane soon shows similar changes, becoming extremely congested, covered with an exudate, and completely opaque. The exudate is at first sero-hemorrhagic, but rapidly becomes thick and purulent, with an admixture of flakes of epithelium and red blood cells. In influenzal cases it may be frankly hemorrhagic.

The course of the disease is variable. First it may run an acute course in a few days, and then rapidly clear up by draining through the Eustachian tube, in marked distinction to the more chronic catarrhal form of otitis media. Secondly, the inflammatory changes in the tympanic membrane may be so severe that softening and perforation occur. Although in exceptional cases the membrane may give way after a few hours, this accident is usually delayed to the third or fourth day of the attack, and occasionally to the end of the second week. Again, thorough drainage of the middle ear through the perforation may result in rapid recovery with healing of the perforation. Thirdly, the perforation may remain open, with escape through it of the discharge from the chronically inflamed lining membrane. At any moment such a perforation may become obstructed by a mass of inspissated secretion, and the inflammatory fire may flare up again as acutely as ever. In some cases the inflammation subsides and the discharge dries up, the "dry perforation" still remaining open. In chronic inflammatory conditions of the middle ear there is always a great tendency to the formation of granulomatous masses and mucous polypi.

Complications.—As long as the discharge persists there is the danger of certain complications; at any moment the sword of Damocles may fall. The chief of these complications are: (1) acute mastoiditis, (2) extra-dural abscess, (3) meningitis, (4) cerebral and cerebellar abscess, and (5) sinus phlebitis. The direction in which the infection spreads from the middle ear will determine which of the complications is likely to occur.

Acute Mastoiditis.—The mastoid antrum, which is merely the posterior end of the tympanic cavity, is early invaded by the purulent secretion

from the middle ear. Mastoiditis is most likely to occur in otitis media following influenza and the other infective fevers. In the earlier stages the mastoid cells contain no pus, but the lining mucosa is red and intensely engorged. Later the mastoid cells become filled with pus and granulations, and their walls undergo necrosis as the inflammatory process penetrates beneath the mucous membrane. When an abscess forms in the mastoid process it does so usually in the middle and lower parts, and more especially in the superficial portion lying under the cortical layer.

The inflammation may spread outwards, upwards, or backwards. If *outwards*, a periostitis is set up with the formation of pus on the surface of the mastoid process. The pus may remain in the locality of the mastoid, or it may burrow up under the scalp, or it may pass down to the tip of the mastoid, and, spreading along the digastric groove, give rise to a brawny swelling under the deep fascia of the neck below the mastoid process, a condition known as Bezold's abscess

If the spread is *upwards* the result will be an extradural abscess, a leptomeningitis, or a cerebral abscess.

Extradural Abscess.—This occurs more frequently as the result of acute than of chronic middle ear suppuration. The pus collects between the dura and the bone in the middle cranial fossa It may remain remarkably localized for a considerable time, but eventually it will begin to spread. The abscess may communicate with the tympanic cavity by a fistulous opening. In other cases, and these are the more dangerous, no evident communication can be detected; indeed the surface of the bone may be quite intact, the infection having spread upwards along the veins or lymphatics.

Meningitis.—The first indication that the course of an acute otitis media is to be complicated may be the development of meningitis. On the other hand meningitis may be superadded to any of the other complications already enumerated. The infection may spread to the meninges via an ulcerated area in the tegmen tympani, but the more usual course is through the internal auditory meatus from an infected labyrinth. As in the case of extradural abscess there may be no demonstrable path of infection from the tympanic cavity to the meninges. There may be a fistulous opening through the dura, or that membrane may be intact. The pus may spread through the subarachnoid space to the base of the brain, or upwards over the cerebral hemisphere as far as the convexity, producing a variety of pressure phenomena. The cerebrospinal fluid shows the changes which have been considered in detail in Chapter XXVIII.

Serous meningitis is a condition in which there is an aseptic accumulation of cerebrospinal fluid in the subarachnoid space and the cerebral ventricles with the production of pressure symptoms. Apart from middle ear disease the condition is one of great medical importance, especially in children, and is greatly benefited by lumbar puncture. In this place, however, we are only concerned with it as a complication of otitis media. It more frequently accompanies chronic than acute inflammation, and appears to be due rather to the irritating action of absorbed toxins than to the presence of bacteria. It may also accompany extradural abscess, cerebral abscess, or sinus phlebitis. The cerebrospinal fluid is under high pressure, but is quite clear, and contains no inflammatory products

Brain Abscess.—There are only two common locations of brain abscess secondary to otitis media, namely the temporo-sphenoidal lobe and the hemisphere of the cerebellum on the side of the middle ear disease. The former is more than twice as common as the latter. Abscesses may occur in other parts of the brain, but are very rare, and must be regarded as metastatic in nature.

The path by which the infection has spread from the ear may be very evident. In other cases the bone may appear normal, but microscopic examination will reveal a suppurative infiltration. In still other cases the bone is quite uninvolved, and infection is due to thrombosis and inward spread along a vein.

The characteristics of a temporo-sphenoidal abscess have already been considered in Chapter XXVIII, and need not be reapitulated here.

Sinus Phlebitis.—The sinus most frequently involved in middle ear inflammation is naturally the lateral sinus which lies along the inner surface of the mastoid process. From there the inflammation may pass down into the jugular vein with disastrous consequences in the shape of metastatic abscesses in the lungs, it may pass to the longitudinal sinus and thus reach the lateral sinus on the other side, or it may spread along the petrosal sinuses to the cavernous sinus. In a case of acute otitis media I found all the cranial sinuses with the exception of the superior longitudinal filled with purulent breaking-down material.

The infection first gives rise to a perisinus abscess, with subsequent inflammation of the wall. The infection may pass direct from the bone to the sinus wall, or may be carried by venous channels. It is remarkable, however, that in cases where extensive destruction of the bone has occurred and the wall of the sinus is bathed in pus, there may be no indication of either phlebitis or thrombosis. In such cases the wall is covered by a thick layer of fibrin which evidently provides an efficient protection against further spread of the infection.

The inflammatory changes in the lining of the vessel together with the accompanying thrombosis have already been described in Chapter VI.

Gradenigo's Syndrome.—The combination of sixth nerve paralysis with pain in the temporal region on the affected side in the course of suppurative otitis media is known as Gradenigo's syndrome. There is a circumscribed, simple, serous leptomeningitis localized to the tip of the pyramid of the petrous temporal caused by diffusion of the infection. The sixth nerve passes through a minute canal bridged over by a ligament, so that swelling or edema of the canal causes pressure on the nerve and paralysis. The temporal pain is due to involvement of the Gasserian ganglion which lies in a depression on the anterior surface of the apex of the petrous temporal.

Cholesteatoma.—The formation of cholesteatomatous masses in the middle ear is so closely related to the question of suppuration that it may be referred to here. True cholesteatomata are pearly tumors of concentric structure which grow from the brain and the meninges and arise from developmental epithelial inclusions. In chronic middle ear inflammation similar firm, white, lamellated masses composed of epithelial cells cornified and shed off from the mucosa are found attached to the lining of the tym-

panic cavity. These masses may reach a great size and entirely fill the middle ear. They cannot be regarded as true tumors.

A much commoner condition is the formation of soft, friable, cholesteatomatous masses, which make no pretence to arise from the wall of the tympanum. They are composed of masses of shed epithelial cells which have been unable to escape in the discharge owing to insufficient drainage, and which in turn tend to obstruct the perforation in the membrane. Cholesterin crystals may be present in large numbers. Owing to the action of putrefactive bacteria the mass may break down to form a foul-smelling pultaceous material, a condition frequently associated with necrosis and ulceration of the bone and the development of intracranial complications such as cerebral abscess or sinus phlebitis.

Tuberculosis.—Tuberculous inflammation of the middle ear is not so uncommon as used to be supposed. When present it is usually chronic and occurs as a complication of pulmonary tuberculosis. The bacilli reach the middle ear through the Eustachian tube or the lymphatics, rarely by the blood stream. They are only occasionally found in the smears of the discharge.

Varying degrees of destruction may be pr   The mucosa may be converted into caseous material. It may b co pletely ulcerated away, so that the walls of the tympanic cavity a   re In advanced cases the greater part of the petrous temporal and the mastoid process may be destroyed by caries. Death may be due to tuber ilous meningitis or brain abscess.

REFERENCES FOR FURTHER STUDY

Milligan, W., and Wingrave, W.: *Diseases of the Ear*. London, 1923

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